DIABETES

The Journal of the American Diabetes Association

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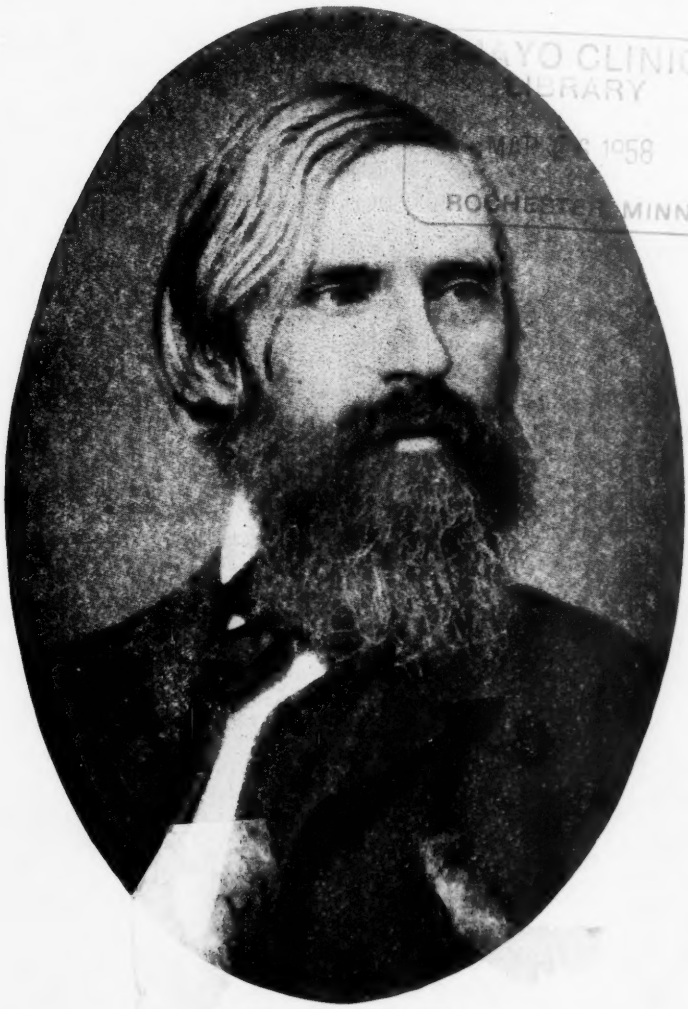

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VOLUME 7, NUMBER 2

MARCH-APRIL 1958

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Hypoglycemic Actions of Phenethyl-, Amyl-, and Isoamyl-Diguanide

Robert H. Williams, M.D., Donald C. Tanner, M.D., William D. Odell, M.D

Seattle

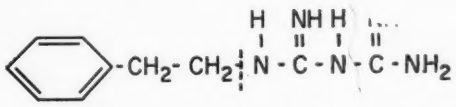
Phenethyldiguanide* (PEDG), a drug capable of producing hypoglycemia,[1,2] has recently been used in the treatment of diabetes.[3,4,5] This paper will discuss mechanisms by which the compound produces hypoglycemia. It will also evaluate the clinical usefulness of PEDG as well as that of related compounds, amyl- and isoamyl-diguanide (figure 1).

EXPERIMENTAL OBSERVATIONS

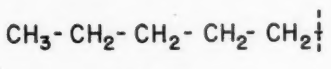
Mechanism of Action of Phenethyldiguanide: PEDG could produce hypoglycemia by causing: (a) wastage of food in urine or feces, (b) decreased gluconeogenesis, (c) increased insulin effect, or (d) increased glucose utilization, other than via insulin. These are considered respectively.

Wastage of Food in Urine or Feces: Hypoglycemia could result from an action comparable to that of phloridzin, but studies have shown that PEDG decreases glycosuria rather than increases it. Whether or not it decreases food absorption has not been reported, but it can cause a profound hypoglycemia in animals fasted for more than forty-eight hours and can also cause it in eviscerated animals. Therefore, mechanisms other than decreased food absorption must be very important.

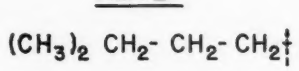
Decreased Gluconeogenesis: PEDG produces a marked decrease in liver glucose output,[2] the hepatic vein glucose becoming equal to that of the portal vein and vena cava. This is due neither to inhibition of glucose-6-phosphatase nor to increased storage of liver glycogen.[6] Indeed, in fasting guinea pigs, PEDG causes a marked depletion of liver glycogen, and this is not replenished even after administration of a large quantity of alanine.[6]



PHENETHYLDIGUANIDE (PEDG)



AMYL-



ISOAMYL-

FIGURE 1

The very low content of glycogen in the liver of guinea pigs so treated may account for the failure to obtain an increase in blood glucose concentration following glucagon and epinephrine.[2]

Since the foregoing studies suggested that PEDG decreases gluconeogenesis, nitrogen balance studies were conducted. A decrease was observed in both nitrogen excretion and urea formation.[6,7] However, as shown in the following experiment, PEDG administration caused the liver glycogen to remain at a subnormal level in spite of the administration of a large dose of glucose (figure 2).

Fifteen guinea pigs were allowed to feed for two hours twice daily for two days, and were then fasted for forty-eight hours. After this, they were divided evenly into three groups. Each animal in one group was injected subcutaneously with 20 mg./kg. of PEDG. Thirty minutes later this and another group were injected subcutaneously with 5 per cent glucose in saline (2 gm./kg.). The third group was given saline alone. The animals treated with PEDG were sacrificed 2½ hrs. later and the glycogen content of each liver was measured.

Presented in large part at the Seventeenth Annual Meeting of the American Diabetes Association on June 2, 1957, in New York City.

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*This compound has also been designated as DBI, phenethylformamidinyliminourea and phenformin.

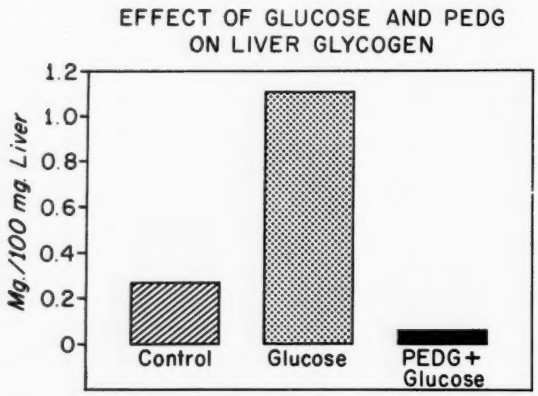

FIG. 2. The liver glycogen is expressed in terms of the amount of glucose liberated from glycogen.

A comparable experiment was done in which a smaller dosage (15 mg./kg.) of PEDG was given. This amount proved to be less effective in depressing the glycogen content and produced much less hypoglycemia.[2]

Whereas the foregoing studies suggest that PEDG decreases gluconeogenesis and thereby produces hypoglycemia, this is not its only mechanism, since in PEDG-treated, hepatectomized guinea pigs it produces a much greater hypoglycemia than that found in untreated hepatectomized animals.[2] This led to a consideration of the drug's effect on the supply of insulin.

Increased Insulin Effect: As reviewed recently,[8] there is much to suggest that tolbutamide increases insulin secretion and, therefore, the role of the pancreas in PEDG hypoglycemia was studied. It was found that although PEDG did produce a definite hypoglycemia in depancreatized[2] and in alloxanized animals,[1] it had a much greater effect on intact animals.

The question then arose as to whether the drug decreased the degradation of insulin caused by "insulinase." Whereas large quantities of PEDG (12 mM/L.) caused significant inhibition of degradation of insulin in vitro, doses sufficient to produce marked hypoglycemia caused only slight inhibition in vivo.[2,6] Moreover, as will be shown in the next section, though certain of the actions of PEDG and insulin are similar, the two differ in many respects.

Increased Glucose Utilization: Whereas PEDG, like insulin, increases the glucose uptake in the rat diaphragm,[6] it is unlike the hormone in that it may lead to a decrease in the glycogen concentration rather than an increase. The question now arises as to whether the drug causes an increased rate of glucose oxidation. In guinea pigs treated with PEDG followed by glucose-C^{14}, there was no increase in the CO_2 or $C^{14}O_2$ expired.[9] However, through the aid of Dr. Robert H. Silver, it was found that there was an increase in respiratory quotient (R.Q.). After subcutaneous injection of 20 mg./kg. of PEDG in three guinea pigs, the R.Q. values were as follows, with the respective control volumes in parentheses: Initial, 0.77±.03 (0.76±.02); forty minutes, 0.78±.02 (0.74±.03); eighty minutes, 0.88±.03 (0.74±0); 120 minutes, 0.98±0.09 (0.75±.02). When 100 mg./kg. of the drug was given, there was an increase in forty minutes from 0.79 to 0.97. Thereafter the animals began to die of hypoglycemia. In eight diabetic patients, with much less accurate facilities available, we have found no change in the R.Q. or oxygen consumption with average daily doses of 150 to 200 mg. of PEDG.

In preliminary experiments on guinea pigs injected subcutaneously with PEDG, diaphragm, adipose tissue and liver slices, removed two hours later and incubated with glucose-C^{14}, were not found to have an increase in radioactivity in the protein or lipid fractions. The question now arising is what happens to the glucose after its rapid disappearance in the muscle?[6] Since PEDG causes lactic acid to accumulate in significant amounts in vitro and in vivo, and since it produces a decrease in CO_2 of diaphragm,[7] it is suggested that the compound promotes anaerobic glycolysis.

Thus, PEDG presumably produces hypoglycemia in two major ways: (a) by increasing anaerobic glycolysis and (b) by decreasing gluconeogenesis. It seems likely that isoamyl- and amyl-diguanide may act similarly.

As recently reviewed by Creutzfeldt,[9] decamethyldiguanidine (Synthalin) has been shown to have many actions like those we have observed with the diguanides (table 1) and, indeed, has been used effectively in the treatment of patients with diabetes. However, certain investigators demonstrated that it was toxic to the liver and kidneys. Such damaging effects have not been found with some of the other diguanides studied.[10,11,12,13] For example, p-chlorophenyl-iso-propyl-diguanide acetate (Paludrine) has been studied extensively and has been considered one of the safest of all the effective antimalarial compounds. Another diguanide, 1:6-di-4′-chlorophenyldiguanidohexane, given to rats for one year, was relatively nontoxic.[18] Moreover, the observations made with phenethyl-, isoamyl- and amyl-diguanide have not demonstrated significant toxic effects.[1-7,10,11] Because of special interest in the possible toxic effects of amyl-diguanide, the following studies are detailed.

We injected seven young guinea pigs subcutaneously twice daily for five and one-half weeks with 10 mg. (per kg. of body weight) of the drug in 1 per cent acacia.

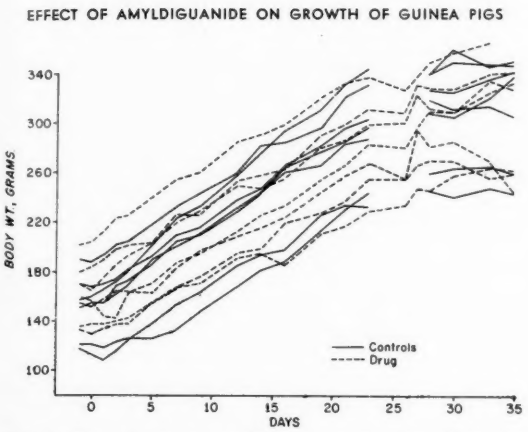

FIG. 3. The animals were weighed every two days. Note that the weight gain was comparable in the treated and the untreated animals.

This dosage is larger, on a per body weight basis, than that used clinically. Seven controls were injected with the same constituents, excluding the diguanide. As can be seen in figure 3, the drug-treated groups gained weight at the same rate as the untreated ones. Occasionally, certain of the treated animals developed the clinical picture of hypoglycemia but rapidly responded to food. No significant alteration was found at autopsy examination of all the abdominal and thoracic viscera, and histological examination kindly made by Dr. Paul Griffith (Assistant Professor of Pathology) of the liver, kidney, spleen, pancreas, adrenal and gastrocnemius revealed no toxic effect. However, after carefully weighing the liver, left kidney, both adrenals and the thyroid, it was found (table 2) that the adrenals of the drug-treated group were enlarged. This presumably was a response to the hypoglycemia. The livers showed borderline enlargement, but there was no increase in the weights of kidney or thyroid. Therefore, there was no evidence of anatomical damage.

TABLE 1

Comparisons of some hypoglycemic compounds

	PEDG	Synthalin	Insulin	Tolbutamide
Hypoglycemia				
without pancreas	+	+	+	0
without liver	+	+	+	+
Glucose uptake*	inc	inc	inc	0
Muscle glycogen*	dec	dec	inc	0
Liver glycogen	dec	dec	±	inc
Liver glucose output	dec	dec	dec	dec
Glucagon hyperglycemia	0	0	+	+
Epinephrine hyperglycemia	0	0	+	+
Glucose oxidation	0	?	inc	inc
Respiratory quotient (man)	0	—	inc	0
Lactic acid†	inc	inc	inc	±
Permanent damage (man)‡	0	+	+	0
Alpha cell damage	0	+	0	0

*Diaphragm in vitro.
†Presumably by anaerobic glycolysis in muscle.
‡No permanent damage has been demonstrated to occur in man from PEDG or tolbutamide therapy, but some may appear with extended studies. Synthalin has caused hepatic and renal alterations. The most severe permanent damage from insulin is found in the central nervous system and is associated with severe hypoglycemia. Of course, the other compounds presumably could cause the same type of damage if they caused as severe and as prolonged hypoglycemia, but so far they have not shown this inclination.
+ signifies a positive response.
0 signifies a negative response.
inc signifies an increased response.
dec signifies a decreased response.

Many of these changes occur only under certain special conditions. The conditions for study of the various phases differed, but those for any one phase were relatively comparable. Except where indicated differently, the studies were with intact animals.

TABLE 2

Effect of amyl-diguanide on organ weight*

	Adrenals mg.	Thyroid mg.	Left kidney mg.	Liver gm.
Control	34.4±5.6	13.3±1.8	500±37	3.0±0.3
Amyl-diguanide	50.2±6.9	14.2±2.3	550±54	3.7±0.3

*All organ weights are indicated per 100 gm. body weight.

CLINICAL STUDIES

Details concerning our investigations on the use of phenethyl-, isoamyl- and amyl-diguanide in diabetic patients will be reported later. The present general comments are based on preliminary observations made while treating twenty-six patients with PEDG, twenty-five with isoamyl-diguanide and fifteen others with amyl-diguanide. For certain patients, each of these compounds has been more effective in controlling diabetes than either tolbutamide or insulin. In other instances, however, control has been less successful. Our own experiences, as well as those of others,[3,11] indicate that the diguanides are more effective in juvenile diabetes than is tolbutamide. In some cases the combined use of insulin and a diguanide has given smoother control than either one alone.

The chief untoward effects of the diguanides are anorexia, nausea and/or vomiting. These symptoms have occurred, so far, in approximately one-third of the patients and are related somewhat to the size of the dose. Few patients experience such symptoms with 100 mg. daily, or less of PEDG or amyl-diguanide, or with less than 200 mg. daily of isoamyl-diguanide. However, doses

larger than these are required in most subjects for control of the diabetes, and the higher the dosage, the greater the percentage of those who will experience side effects. There is a significant individual variation in susceptibility to these effects; some patients can take with impunity doses several times the amount which would cause unbearable nausea in others. Upon cessation of therapy, the ill effects subside within a day or two, and no further sequelae are observed. Isoamyl-diguanide is less satisfactory than either of the other agents in that it causes nausea and/or vomiting more frequently and exerts less complete control of diabetes. Whether or not amyl-diguanide will prove to be superior to PEDG, which we consider a possibility, depends upon the results of further studies; these are now under way.

Frequent evaluations of liver and kidney function in these diguanide-treated patients, and careful observations of the patients during the course of treatment, have failed to demonstrate any other significant untoward reactions. However, much more extensive investigations will be required to determine the net usefulness as well as the hazards which may be involved in this type of therapy.

SUMMARY

Studies are reported suggesting that phenethyl-diguanide lowers blood sugar by (a) promoting anaerobic glycolysis, with increased glucose utilization and (b) by causing decreased gluconeogenesis, with a decrease in the output of glucose from the liver.

In preliminary investigations using phenethyl-, isoamyl- and amyl-diguanide in the treatment of diabetes, each has appeared preferable to tolbutamide or insulin in some patients. Nausea and/or vomiting occur relatively frequently and, when they do, cessation of diguanide therapy may be indicated. No other significant ill reactions from these drugs have been observed. Some patients have never experienced side effects in spite of relatively large doses. Isoamyl-diguanide appears less satisfactory than the other diguanides.

Much more extensive investigation will be required to determine the net usefulness as well as the hazards of this type of therapy.

SUMMARIO IN INTERLINGUA

Le Actiones Hypoglycemic De Phenethylo-, Amylo-, E Isoamylo-Diguanido

Es reportate studios que pare indicar que phenethylo-diguanido reduce le sucro del sanguine per (a) promover glycolyse anaerobi—con le effecto de un augmentate utilisation de glucosa e (b) causar un retardo del gluconeogenese—con le effecto de un reducite rendimento hepatic de glucosa.

Investigationes preliminari con phenethylo-, isoamylo-, e amylo-diguanido como medicationes anti-diabetic ha monstrate que omne iste compositos es a preferer a tolbutamido e a insulina in certe patientes. Nausea e/o vomito occurre con relativemente alte frequentias. In lor presentia, cessation de diguanido es possibilemente indicate. Nulle altere significative reactiones adverse ha essite observate in le uso de iste drogas. Il ha patientes qui ha nunquam experientiate ulle effectos lateral in despecto de relativemente alte doses. Isoamylo-diguanido pare esser minus satisfactori que le altere diguanidos.

Multo plus extense investigationes es requirite pro determinar le utilitate nette como etiam le riscos de iste typo de therapia.

ACKNOWLEDGMENTS

We are very grateful to Dr. Georges Ungar and Dr. Louis Freedman of the U. S. Vitamin Corporation for the generous supply of the compounds and for other aid. We also appreciate the kind assistance given by Dr. Paul Hyde, Dr. Hiromichi Narahara, Dr. Henry Tomizawa, Dr. Jean Tyberghein and Miss Maureen O'Connell.

These investigations were aided by grants from the Atomic Energy Commission, the U.S. Public Health Service, the Warren Orr Fund and the U. S. Vitamin Corporation.

ADDENDUM

Additional studies have revealed that approximately two-thirds of our patients have experienced untoward reactions to diguanide therapy. Slightly more than one-half observed the gastrointestinal complaints that have been mentioned. Approximately one-third of the patients taking this therapy for more than one month lost a few pounds in body weight, but this was regained rapidly upon substituting insulin for the diguanide. No permanent ill-effects of any type have been observed.

Continued observations are necessitated for the most accurate appraisal of this type of therapy. At present it appears that it has a very limited field of usefulness, but it has exhibited significant merit in certain subjects, particularly brittle diabetics. An important objective is to determine whether some of the untoward effects can be eliminated while preserving the benefits—such is a possibility.

Steiner et al. have recently found that phenethyldiguanide significantly inhibits cytochrome oxidase. This could account for many of the biochemical changes described in this paper.

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GROUP DISCUSSION OF THE PRECEDING PAPER AND OF "CLINICAL TRIALS WITH DBI, A NEW (NON-SULFONYLUREA) ORAL HYPOGLYCEMIC AGENT," BY LEO P. KRALL, M.D., AND RAFAEL CAMERINI-DAVALOS, M.D.

JULIUS POMERANZE, M.D., (*New York City*): Our problem, as the first clinical investigators with phenylethylbiguanide (DBI), was to establish a proper clinical dose and indicate absence of toxicity. Oral and intravenous glucose tolerance curves in normal and diabetic subjects established that 100 mg. of DBI orally had a sugar lowering effect. They also showed some evidence of increased peripheral utilization of glucose. (*Proc. Soc. Exp. Biol. & Med.* 95:193-94; Scientific Exhibit, AMA Annual Meeting, June, 1957.)

We have had more than fifty patients under study for eleven months. A young male diabetic was the first patient started with the drug. He was poorly controlled with 70 to 80 units of insulin per day. Two hundred fifty milligrams of DBI and 20 units of insulin effectively controlled the diabetes.

During the course of treatment, this patient on two occasions experienced severe hypoglycemic reactions with nausea and vomiting. He rapidly recovered following glucose therapy and readjustment of insulin and DBI dosage. Repeated liver function studies and renal and hematologic studies showed no evidence of any damage having been done during these severe episodes, or by the continuation of the drug for a period of eleven months.

We have two other young diabetics who are receiving 150-200 mg. per day of this drug for periods up to six months without insulin. This drug is effective in the juvenile type of diabetic, although exogenous or endogenous insulin is probably required. We also have patients who have had diabetes for as long as twenty-eight years and have responded satisfactorily to the drug without insulin.

I think it is important at this time to enumerate both the disadvantages and advantages of the drug. The disadvantages, of course, are the side effects, the occasional severe hypoglycemic reaction and the ketosis following the vomiting incurred by the use of the drug.

The advantages, of course, are the oral administration of the drug, its effective hypoglycemic effect without any evidence of toxicity to date, its effectiveness in the young diabetic patient, especially in helping to smoothen their course. The labile patient, who is not easily controlled with insulin dosage, can be better controlled with supplemental use of the drug. It has always been my hope that in the treatment of diabetes, something may become available to control the degenerative as well as the biochemical aspects of the disease. This may not be such a drug, but studies such as this may develop a drug which will have this desirable effect on the degenerative changes.

THOMAS H. MCGAVACK, M.D., (*Martinsburg, West Virginia*): In connection with the use of DBI I would like to emphasize the word of caution that was implied in the data on one of the slides shown by Dr. Krall. We have followed about twenty patients to whom this drug has been given. It was quite difficult to determine the effective dose in any given subject, without running the chance of hypoglycemia on the one hand, or acidosis on the other. In other words, the toxic and therapeutic

dosages seem very close together.

Our second objection to DBI is the high incidence of side effects; three-fourths of our patients developed one or more toxic symptoms, chiefly of a gastrointestinal nature.

In the third place, we have seen acidosis occur in the presence of normoglycemia and aglycosuria. This occurred without warning in one individual. I think we must proceed with the utmost caution in the clinical use of this drug.

HENRY T. RICKETTS, M.D., (*Chicago*): Despite the very interesting clinical and experimental observations that have been presented, I have not heard enough yet to satisfy me concerning extensive animal experimentation with these drugs, with a better delineation of long-term toxicities, MLD's and so on. I wonder if those who have been using this drug have any background in this respect, and if so, would they please give it.

GARFIELD G. DUNCAN, M.D., (*Philadelphia*): I am especially interested in the results of DBI therapy in the case of one of the juvenile patients reported by Dr. Krall. It is not rare to see all detectable evidences of diabetes disappear temporarily in adequately treated young patients only to find the diabetes return in a more severe and permanent form after a short period. I would like to ask whether or not DBI had been discontinued. If so, did hyperglycemia and glycosuria appear promptly? If this were not done, proof of the effectiveness of DBI would be lacking in this case. Furthermore, if DBI therapy was uninterrupted and hyperglycemia and glycosuria recurred, this might be interpreted as an indication of decreased effectiveness of the drug when in fact it would probably indicate the end of the short remission sometimes seen in these patients when no drug therapy was involved.

GEORGES UNGAR, M.D., PH.D., (*New York City*): I would like to answer Dr. Ricketts' question since I have been doing most of the animal work with DBI, besides Dr. Williams' group.

We have tried DBI in the following species: guinea pigs, rats, mice, rabbits, Rhesus monkeys, cats and dogs. With the exception of the dog, all species responded with hypoglycemia. Monkeys and guinea pigs are the most responsive animals.

There are great difficulties involved in evaluating the toxicity of a hypoglycemic drug. Like insulin, DBI could be considered as a highly toxic material since both kill the animals by hypoglycemic shock. This, however, is not a truly toxic effect since it is inherent in the pharmacological action itself.

The best we could do was to give DBI at dose levels which lower blood sugar by about 30 per cent. We have done this in guinea pigs, rats and monkeys for varying periods of time without producing any toxic symptoms or any biochemical, hematological or histological changes. At the end of this year, when the results of a six months' toxicity test are available, we can make a more definite statement.

ROBERT H. WILLIAMS, M.D., (*Seattle*): With regard to Dr. McGavack's comment relative to ketosis, I wish to state that even after prolonged observation we have observed no ketogenic effect of PEDG in any patient. Ketosis was observed in two subjects but this apparently occurred in spite of therapy rather than due to it. Guinea pigs kept fasting for four days and injected with large doses of PEDG did not develop any more acetonuria than the controls.

With respect to Dr. Duncan's comment relative to stopping and starting the PEDG therapy periodically, I wish to state that we have done this many times and have frequently switched to other oral compounds. It is clear that the biguanides significantly lower the blood sugar in many patients.

LEO P. KRALL, M.D., (*Boston*): Dr. McGavack, I agree perfectly that it is a very difficult drug to use. It certainly has many uncertainties that occur quite suddenly. I also agree that the therapeutic dose and that level which causes side effects are fairly close. As yet, we have no proof that the therapeutic dose is anywhere near the toxic dose, if any.

Dr. Ricketts, I regret there is no more information available concerning the animal experimentation, which has been under study for some two years by Dr. Georges Ungar. Dr. Julius Pomeranze has liver function studies on patients receiving DBI for ten to twelve months with no abnormal findings.

Dr. Duncan is correct about the juvenile diabetes, of course. No one can disagree with that. This case cited was given placebo during which period the blood sugar became elevated. She received insulin when she came into the hospital for three or four days. For all practical purposes, you might assume that she is relatively an untreated diabetic and certainly not the severest type. At this time we cannot fully evaluate this drug nor can we compare this with other drugs. It is far too early for that. We merely limited ourselves to watching patients, trying to work out dosage schedules, observing the blood sugar lowering effect, and trying to follow the earliest possible evidence of toxicity.

You must remember that these observations have been taking place for only six months and with only fourteen patients.

Complete Remission of Severe Diabetes

Franklin B. Peck, Jr., M.D., W. R. Kirtley, M.D., and Franklin B. Peck, Sr., M.D.

Indianapolis

The life history of diabetes is characterized by its chronicity. Joslin[1] warns against speaking of "cures," and states that the tendency to diabetes is inborn and must remain so for life. Ricketts[2] has defined diabetes as "a chronic hyperglycemia and, usually, glycosuria which may be either continuous or intermittent and is due to a relative or absolute deficiency of insulin. Its typical form in man is associated with an hereditary tendency." Ineffaceable permanency is thus inherent in our present concept, and with it we agree.

Fluctuations in the severity of the diabetic state, particularly when measured by the quantity of insulin required to maintain carbohydrate equilibrium, are well known, and their causes are usually obvious, as changes in weight, dietary intake, fever, infection, muscular activity and endocrine disturbances. An apparently sudden onset of diabetes has been described, usually in younger persons, but it is more likely to be a sudden discovery of a condition previously existing. The dramatic, abrupt cessation of all manifestations of profound diabetes and coma in one of our patients with disappearance of severe insulin resistance within a period of a few days was, however, singularly striking, and without parallel in our experience. Until proven otherwise it is to be regarded as an unusual if not unique remission.

Since preparing this report, another case somewhat similar has been described by Harwood.[3] His search of literature fails to show other cases of recovery *after acidosis* in adults. The remission in his case is attributed to strict controls of glycemic levels within normal bounds by means of diet and insulin. We concur in his opinion that these measures should make remissions a more common occurrence.

CASE REPORT

R.W. (325653), a forty-one-year-old Negro male, was admitted to the Emergency Ward of Indianapolis General Hospital on Oct. 12, 1954, in profound diabetic coma. He had been in good health until one week before admission, when he had an upper respiratory infection, loss of appetite, and loss of weight. There is no history of diabetes in the family. The day before admission he remained at home because of nausea and vomiting, and was found unconscious.

The physical findings were of a patient in deep coma and a shock-like state, with Kussmaul respiration and an acetone odor to his breath. The eyeballs were soft and funduscopic findings were normal, as were the lungs, heart and abdomen. Generalized hypoactive deep reflexes were noted, and there was no response to painful stimuli. The blood pressure was 0-80/60 mm.Hg., pulse 120, respiration 32.

The urine was strongly (4 plus) positive for sugar and acetone. Blood sugar was 1,280 mg. per cent (Somogyi method); plasma CO_2 was 3 m.Eq. and blood urea nitrogen 60 mg. per cent. Calculation of the Rabinowitch severity index gave a numerical value of twenty-four (any rating of twenty-one or over is exceptionally severe and carries with it a mortality rate of 80 to 90 per cent).

Vigorous treatment over the first twelve hours necessitated venous incisions in the lower extremities in order to combat circulatory collapse by intravenous infusions with norepinephrine added to maintain the blood pressure. The progress of therapy during this period is summarized in figure 1. Note that 1,910 units of insulin were administered, and a total of 6.5 liters of normal saline, 2 liters of 5 per cent dextrose and 65 m.Eq. of potassium. It was on the advice of Dr. D. D. Van Slyke, who was visiting our laboratories that day, that an additional 15 gm. $NaHCO_3$ was given intravenously as the patient was obviously not responding to treatment. In retrospect, we believe this was probably lifesaving, as the CO_2 values then began to rise, and the patient's general condition began to improve. During the hours when blood pressure was minimal, pressure of the patient's weight on his buttocks resulted in a large area of sacral decubitus which subsequently required surgical debridement before healing occurred. Unconsciousness persisted for two full days. Electrolyte balance was greatly disturbed, the serum sodium being 170 mEq., with serum chlorides 138 m.Eq. despite adequate urinary output. It was thought at the time that this might be the result of too vigorous administration of sodium chloride, although adequate urinary output was present during most of the stormy initial course.

The patient responded poorly during the first few days. Weakness of the left arm and leg was noted, which in conjunction with the altered electrolyte pattern suggested cerebral thrombosis. Spinal fluid was normal. Insulin resistance appeared on October 14, subsequently requiring 200 to 400 units daily in order to maintain normal glycemia (figure 2). Regulation of glycemia between 70 to 90 mg. per 100 ml. of blood sugar was finally established with 90 units NPH insulin per day. A severe insulin shock occurred on the fifth day, with blood sugar of zero, and another insulin shock occurred on the tenth day. There was prompt response to glucose intravenously and

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From the Lilly Laboratories for Clinical Research, Indianapolis, Indiana.

FIGURE 1

Cumulative coma record (R.W. 325653)

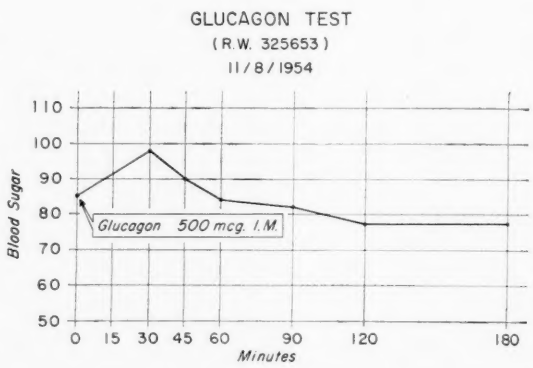
Date	Time	Blood Pressure	Urine Volume	Urine Sugar	Urine Acetone	Blood Sugar	Blood CO_2	Insulin	K	Na	Cl	Fluids, etc.
10/12	11:30 A.M.	0-80/60	20	4+	4+	1,280	3 m.Eq.	180				1,000 cc. saline and Levophed
	1:30 P.M.	130/70	20	4+	4+	1,288	6.3	510				2,000 cc. saline and Levophed
	4:00 P.M.	112/60	250	4+	4+	766	8.9	1,510	3.6	150	126	5,000 cc. saline and (5 P.M.–15 gm. $NaHCO_3$)
	8:00 P.M.	110/70	1,350	4+	2+	322	14.1	1,910				6,600 cc. saline 2,200 cc. 5% dextrose 65 m.Eq. K (dep. S-T)
	10:00 P.M.	100/60	1,500	1+	2+	240	23.4	1,910				
10/13		140/90		0	0	148	24	10 c 30 NPH	3.8	170	138	

FIGURE 2

Blood sugar record (R.W. 325653)

Date	Insulin	Blood Sugar
10/14/54	310	148-294
15	310	215-348
16	440	366-205-0
17	160	254
18	100	188
21	100	152
25	100	96
29	100	100
11/1	90	60
11/5	90	80-90
11/7-23	90	67-96
11/24-27	30	62-90
11/28-1/7	0	67-104
1955	0	79-95
1956	0	85-106
1957	0	84-107

FIGURE 3



then several days of satisfactory regulation with 30 units of NPH insulin daily. The patient was transferred to the Lilly Research Ward on Nov. 3, 1954, for further study of his metabolic state. Clinical evidence of diabetes completely disappeared.

Insulin was entirely discontinued on November 27. The blood sugar level remained normal in both fasting and postprandial periods. The decubitus healed under treatment with penicillin and Varidase. A glucagon test (figure 3) gave a lower-than-normal blood sugar elevation (usually 30 to 40 mg. per cent by our methods). Oral glucose tolerance tests and a triple glucose tolerance test (figure 4) consisting of two orally administered priming doses followed by an intravenous glucose curve were essentially normal except for delayed return in two hours. In fact, a sharp hypoglycemic reaction occurred one and one-half hours after the intravenous glucose. This "Staub-Traugott" phenomenon[4] appears in normals, and the less severe the diabetes, the more nearly does the curve approach normal.[5] An insulin tolerance test displayed some initial slight delay in responsiveness to insulin (figure 5), but was otherwise within normal limits. The glucose-insulin tolerance test was not abnormal (figure 6), since in normals the hyperglycemia is greater than after the administration of the same amount of glucose without insulin, ranging from 25 to 75 per cent increase from initial blood sugar values.[6] The Thorn eosinophil test for adrenal function was normal.[7] Three basal metabolic rates were within normal limits. A four-day ACTH stimulation test[8] (figure 7) did not show a normal increase in 17-ketosteroids and 11-oxysteroids in the urine. Later a high eosinophil count (50 per cent) was attributed to his long-term penicillin-Varidase therapy, and the count fell rapidly toward normal limits when these agents were discontinued. Skull films of sella turcica were normal, the blood count, liver and kidney function studies were all within normal limits. Evidence of the initial severe diabetes having disappeared, the patient was released to the outpatient Diabetes Clinic for long-term observation, with instructions to maintain his diet within the range of 1,500 to

FIGURE 4

GLUCOSE TOLERANCE TESTS

(R.W. 325653)

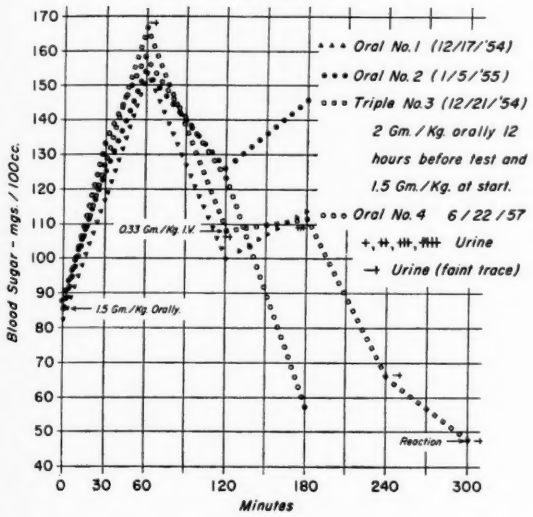
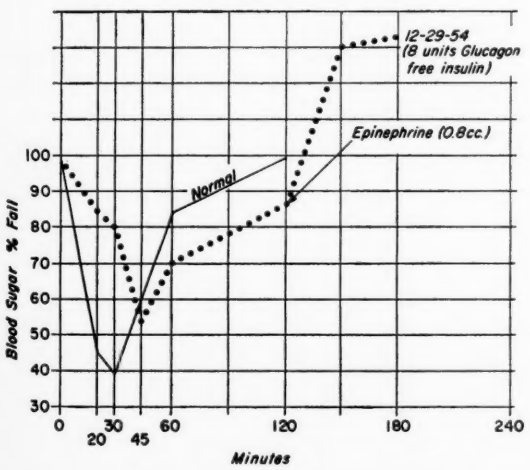

Oral No. 1 (12/17/'54)
Oral No. 2 (1/5/'55)
Triple No. 3 (12/21/'54)
2 Gm./Kg. orally 12 hours before test and 1.5 Gm./Kg. at start.
Oral No. 4 6/22/57
+, ++, +++, ++++ Urine
→ Urine (faint trace)
0.33 Gm./Kg. I.V.
1.5 Gm./Kg. Orally.
Reaction
Blood Sugar - mgs. / 100cc.
Minutes

FIGURE 5

INSULIN TOLERANCE TEST

(R.W. 325653)



1,800 calories to avoid gain in weight.

Subsequent visits to the Diabetes Clinic have confirmed the continued absence of any signs or symptoms of diabetes. The blood sugar levels have remained entirely normal since 1954, and there has not been a single positive test for glycosuria, either in the clinic or under home and working conditions.

Periodic rechecks of the patient's glucose tolerance have been continued. The most recent of these is shown in figure 4 (June 22, 1957). Further evidence of the dormant nature of

FIGURE 6

GLUCOSE-INSULIN TOLERANCE

(R.W. 325653)

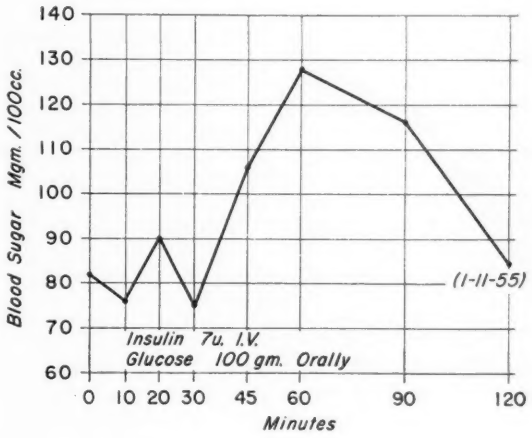


FIGURE 7

ACTH stimulation test (R.W. 325653)

Date	Vol.	ACTH	17-Keto.	11-Oxy.	Creat.
1/2/55	1,700	No	21.2 mg.	3.4 mg.	1,696 mg.
1/4/55	1,550	20 I.U.	31.8 mg.	0.8 mg.	1,519 mg.
1/5/55	1,320	20 I.U.	11.4 mg.	2.1 mg.	1,526 mg.
1/6/55	2,120	20 I.U.	21.7 mg.	1.7 mg.	1,865 mg.

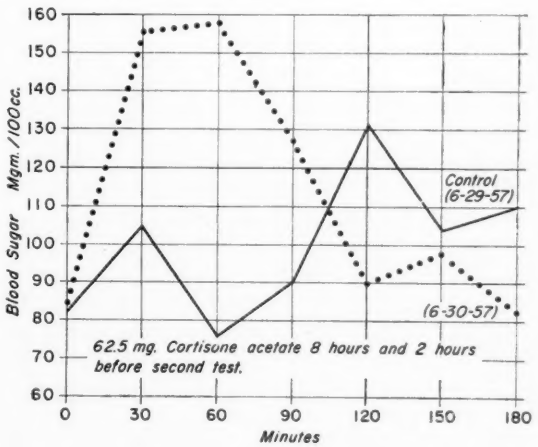
BMR −1, −1, −9

Liver and kidney function studies were normal.

FIGURE 8

FAJANS-CONN C-G. TOLERANCE TEST

(R.W. 325653)



the diabetes in this case is shown by the response to the cortisone-glucose tolerance test of Fajans and Conn,[9] performed according to their methods on June 29-30, 1957. The findings are outlined in figure 8.

The control curve taken on the day before the cortisone was administered was well within the limits of normal glucose tolerance except for a secondary rise not observed on previous tests. It somewhat resembles the rise in the glucose-insulin tolerance test, and we have no explanation for it. Fajans and Conn[9] regard the combination of a one-hour value of 160 mg. per 100 cc. or above plus a two-hour value of 120 mg. or above as diagnostic of the existence of the diabetic state. Their third criterion is that the level at ninety minutes be above 140 mg. per 100 cc. to be diagnostic of diabetes. None of the levels in our case exceed these limits, and we must consequently regard the cortisone provocative test as failing to uncover a latent or hidden diabetes in this instance.

DISCUSSION

These data establish beyond question the occurrence in this case of an exceptionally severe and acute diabetes accompanied by profound ketosis, circulatory collapse, and concomitant alterations in fluid and electrolyte balance so characteristic of such a state. In addition there was a striking insulin resistance during the early phases.

The subsequent disappearance of any clinical manifestations has not been accompanied by significant weight loss. Ordinary glucose tolerance tests show only a slight delay in return to the starting value at the second hour. There was a slight delay in hypoglycemic response to an intravenous test dose of insulin. These constitute the only remaining evidence of any abnormality remaining, and a latent defect is not brought out by the Fajans-Conn test after a three-year period.

Joslin[3] has stressed the criteria for recovery from diabetes as follows: "Glycosuria and hyperglycemia should be absent, while the patient is without diabetic medication, both before and an hour after a meal. This meal must contain at least two-fifths of the carbohydrate for the day. The carbohydrate for the twenty-four hours should comprise at least two-thirds of the calories necessary to provide thirty calories per kilogram body weight. Better still, the carbohydrate tolerance should be unimpaired as judged by a normal glycemic curve following the oral administration of 100 gm. of glucose to the patient in the postabsorptive state. A diagnostically proved case of diabetes of one or more months duration, which conforms to the test for recovery at the beginning and end of an interval of five or more years, shall be considered cured." The last of these criteria has not yet been met as the term of remission is only three years. Of special interest, however, is the failure to respond to the cortisone test.

We have no explanation for the bizarre behavior of the diabetes in this case. In personal discussion Dr. R. D. Lawrence of London mentioned only one rather similar instance—in a patient who was later found to have experienced a pancreatic thrombosis with later resolution disclosed at autopsy. Such manifestations as these must be very rare.

SUMMARY

The findings are reported in a forty-one-year-old male admitted to the hospital on Oct. 12, 1954, in severe diabetic coma. There was no history of diabetes until the onset of illness one day before admission, when he was found unconscious. On admission the blood sugar was 1,280 mg. per cent, CO_2 was 3 m.Eq., the Rabinowitch Severity Index was 24, and the patient was in circulatory collapse. Nineteen hundred and ten units of insulin were administered during the next twelve hours, and subsequently insulin resistance developed requiring 200 to 400 units of insulin daily in order to maintain normal glycemia.

After approximately ten days in the hospital responsiveness to insulin suddenly improved and severe hypoglycemia ensued. Regulation was then established with 90 units of NPH insulin, which was reduced to 30 units daily until Nov. 27, 1954, when insulin was entirely discontinued and the patient's blood sugars remained normal. Intensive study of the patient's endocrine and metabolic status subsequently disclosed no significant abnormalities, and clinical evidence of diabetes is not revealed even to the provocative cortisone-glucose tolerance test of Fajans-Conn. The case represents an unusual instance of temporary severe diabetes accompanied by coma and acidosis with apparently complete recovery as far as can now be determined. Until a five-year period has elapsed, it should be regarded as a remission rather than a cure.

SUMMARIO IN INTERLINGUA

Remission Complete de Diabete Sever

Es reportate le constatationes facite in le caso de un masculo de quaranta-un annos de etate qui esseva admittite al hospital le 12 de octobre 1954 in un stato de sever coma diabetic. Le patiente non habeva un historia de diabete ante le declaration del morbo un die retro quando ille habeva essite trovate in stato de inconscientia. Al tempore del hospitalisation le valor pro sucro del sanguine esseva 1.280 mg pro cento, illo pro CO_2 esseva 3 mEq, le Indice de Severitate de Rabinowitch esseva 24, e le patiente se trovava in stato de collapso circulatori. In le curso del sequente dece-duo horas, 1910 unitates de insulina esseva administrate. Subsequentemente resistentia a insulina se disveloppava, requirente

200 a 400 unitates de insulina per die pro mantener nivellos normal de glycemia.

Post circa dece dies al hospital, le responsa a insulina se meliorava subitemente con le resultato de un sever hypoglycemia. Regulation esseva establite per medio de 90 unitates de insulina NPH per die. Iste dose esseva reducite a 30 unitates per die usque le 27 de novembre 1954 quando le insulina esseva abandonate completemente. Postea le sucros sanguinee del patiente remaneva normal; intense studios del stato endocrin e metabolic del patiente revelava nulle significative anormalitates; e signos clinic de diabete se manifesta non mesmo sub le conditiones del provocatori test de tolerantia a cortisona-glucosa secundo Fajans-Conn. Le caso representa un exemplo inusual de sever diabete temporari accompaniate de coma e acidosis con restablimento apparentemente complete, in tanto que isto pote esser determinate al tempore presente. Usque al fin de un periodo de cinque annos, le resultato debe esser reguardate como remission plus tosto que como curation.

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Insulin Hypoglycemia in Angina Pectoris

The clinical dictum that hypoglycemic episodes constitute a serious hazard to the patient with angina pectoris has been supported by relatively few case reports. W. C. Judson and W. Hollander (*Am. Heart J.* 52:198 (1956)) have made a systematic attempt to document this impression by studying the reactions of patients with arteriosclerotic heart disease and the anginal syndrome to hypoglycemia induced by insulin.

The eleven patients had typical anginal pain on effort, associated with electrocardiographic evidence of myocardial ischemia. Insulin was injected intravenously, 0.1 unit per kilogram of body weight, and the blood glucose, sodium and potassium were measured at fifteen- to thirty-minute intervals. An electrocardiogram and ballistocardiogram were simultaneously recorded. Some of the patients received hexamethonium in a dose sufficient to produce postural hypotension before the insulin was given.

When intravenous insulin alone was used, the blood sugar fell from an average level of 81 mg. per cent to 38 mg. per cent. The serum sodium did not change but the serum potassium decreased an average of 0.7 mEq. per liter. Seven of the eleven patients showed electrocardiographic changes which were unlike the myocardial ischemic changes produced by exercise. The most common change was a flattening and broadening of the T waves. In none of these patients, however, was anginal pain produced, although they displayed the typical signs and symptoms of hypoglycemia during the test.

When the patients were pretreated with hexamethonium in an effort to prevent the effects due to adrenergic stimulation, the electrocardiographic changes and symptoms were not altered.

The effect of this investigation is thus to show that this degree of hypoglycemia does not cause the electrocardiographic changes of myocardial ischemia in patients with arteriosclerotic heart disease. The electrocardiographic changes were consistent with those attributed to hypokalemia (low blood potassium levels) and the decrease in serum potassium supports this idea. No convincing evidence was obtained to suggest that these changes were due to discharge of the sympatho-adrenal system. Although this study allays some of the fears which have previously been emphasized regarding the close control of diabetic subjects with arteriosclerotic heart disease, it should not be assumed that hypoglycemic shock may not, on occasion, cause adverse cardiovascular effects.

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Sequelae of Arteriosclerosis of the Aorta and Coronary Arteries

A Statistical Study in Diabetes Mellitus

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St. Louis

The relation of diabetes mellitus to arteriosclerosis has recently been summed up by Edwards[1] as follows: "Diabetes is commonly recognized as having a positive influence in coronary atherosclerosis. It is a relatively common experience to perform necropsies on diabetic persons who die of severe atherosclerosis at ages much younger than the average." In the first edition of their book, *Pathology of Diabetes Mellitus,* Warren and LeCompte[2] stated that they had not seen an autopsy on a diabetic patient whose disease had lasted five years or more, free from arteriosclerosis, regardless of age. However, they subsequently encountered a few cases with duration over five years practically free from arteriosclerosis.

The evaluation of the severity of arteriosclerosis appears to be, in large part, a subjective one. It would seem that a more objective approach to the problem would be an evaluation of the frequency of sequelae of arteriosclerosis. For example, White[3] has pointed out that diabetic patients with hypercholesterolemia are fifteen times more likely to develop arteriosclerosis than diabetic patients with normal cholesterol levels, but it has not been established that patients with controlled diabetes have any striking aberrations of the serum cholesterol.[4–6] Despite such considerations it is generally accepted that the positive effect of diabetes on arteriosclerosis is the result of increased serum lipid levels associated with this disease. Strangely, when one evaluates the frequency of sequelae of arteriosclerosis they are peculiarly limited to the heart and extremities, and Warren and LeCompte[2] have pointed out that cerebral arteriosclerosis is no more frequently a cause of death in diabetic patients than in nondiabetics. Furthermore, Blumenthal and coworkers[7–10] have been unable to demonstrate, on a microscopic level, an increased intensity of arteriosclerosis of major arteries in diabetic patients.

On the other hand, it appears to be well established that myocardial infarction and gangrene of the lower extremities are considerably more common in the diabetic population than among nondiabetics. Whether these are truly sequelae of an intensified arteriosclerosis of the main arterial supply (cognate system) or are due to other factors remains to be established. Warren and LeCompte[2] have stated that careful observation of diabetics who have survived ten, fifteen, twenty or more years with their disease makes it increasingly clear that the disabilities in this group are largely referable to disorders of the smaller blood vessels. The lesions affecting these small vessels seem to be fundamentally different from those involving the large elastic and muscular arteries, and in many respects they seem to be characteristic of, if indeed not specific for, diabetes.

The vascular lesions of diabetic glomerulosclerosis and diabetic retinopathy are well recognized as being specific, but this has not been extended to a successful study of other organs with the exception of the placenta. In a recent study of the latter organ in diabetic mothers Burstein, Soule and Blumenthal[11] demonstrated an obliterating endarteritis of placental arteries consisting primarily of polysaccharide deposition and endothelial proliferation which appears to be specific for diabetes. Perhaps the failure to recognize specific vascular lesions in other sites may be due to the fact that they take a different, less easily recognizable form, dependent upon the response potentials of the tissue components that make up the vascular wall. Blumenthal[12] recently proposed a concept of "Response Potentials of Vascular Tissue Components," which constitute determinants in establishing the form which a vascular lesion will take at a particular anatomical location. He has shown that these responses are not uniform throughout the body.

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Because of the foregoing considerations, the possibility exists that the increased susceptibility of diabetics to the sequelae of degenerative vascular disease may be primarily due not to an intensification of arteriosclerosis and occlusion of cognate system arteries, but rather to impairment of the potential for developing collateral circulation because of involvement of small vessels with an obliterative process specific for diabetes. In such an event occlusion of major arteries might occur with equal frequency in diabetics and nondiabetics; or, the intensification of arteriosclerosis of cognate system arteries might be due to a local increase in peripheral resistance because of the pathological process in small vessels. At any rate, occlusion of a large artery would be more frequently disastrous for the diabetic because of inadequate collateral. Such a possibility is suggested by the observation of Thomas and associates[13] that the average age at death from acute myocardial infarction is not significantly different in diabetics than in nondiabetics, although the frequency of such an event is three to four times greater among diabetics.

The present report consists of a statistical study of autopsy cases in which certain data relevant to this problem are presented which have not been reported heretofore, and which suggest a failure to develop adequate collateral circulation in the diabetic patient. It represents a starting point for a comparative study of the collateral circulation in various organs in diabetic and nondiabetic individuals.

MATERIAL AND METHOD OF STUDY

The material utilized in this report consists of 3,470 autopsies performed over a period of about thirty years. During this time all of the necropsies were supervised and reviewed by two pathologists, either the late Dr. S. H. Gray or one of the authors, H.T.B. In this series 1,967 (56.7 per cent) were males and 1,503 (43.3 per cent) females. There were 3,206 nondiabetic patients (92.4 per cent) and 264 diabetics (7.6 per cent). The average age at death of the nondiabetics was 57.9 years and of the diabetics 60.4 years. Among the nondiabetics, males lived two years longer on the average than females, while among the diabetics there was no significant sex difference.

There were 748 cases of coronary thrombosis and/or myocardial infarction, of which 617 were in nondiabetics and 131 in diabetics. The average age at death in the former group was 64.0 years, with an average of 62.3 in men and 67.3 in women; the average age at death in diabetics with coronary thrombosis and/or myocardial infarction was 64.1 years and identical in both sexes.

Of the nondiabetic population 1,842 were males, representing 93.6 per cent of all of the men in this series, and 1,364 were females, representing 90.7 per cent of the women. Expressed in another way, 57.5 per cent of the total nondiabetic autopsies were in males and 42.5 per cent in females, while 47.3 per cent of the diabetic group was made up of males and 52.7 per cent of females. Thus there was a relative predominance of males in the nondiabetic population and of females among the diabetics. The distribution by age and sex is shown in table 1, which also includes the average age at death.

The following types of information were compiled:

1. *Comparative Frequency of Sequelae in the Aorta.* An attempt was made to evaluate the effects of diabetes on the severity of arteriosclerosis by determining the frequency in the two groups of arteriosclerotic aneurysm formation and of atheromatous embolization. The latter is a process in which atheromatous material breaks loose from aortic plaques and is carried by the blood stream to small intraparenchymal arteries, where it becomes embedded in the walls of the latter.

2. *Comparative Frequency of Hypertension.* This comparison included cases with and without thrombotic occlusion of the coronary and/or myocardial infarction. Individuals were considered hypertensive when cardiomegaly was present without evidence of valvular disease. The criteria for cardiomegaly were hearts weighing 350 gm. or more in females and 400 gm. or greater in males; these weights were arbitrarily set at 50 gm. greater than usually utilized for this purpose.

3. *Comparative Frequency of Coronary Thrombosis and/or Myocardial Infarction.* This complication was analyzed as regards frequency, coexisting hypertension, age (healed and/or acute; single or multiple), and the comparative frequency of myocardial rupture and ventricular aneurysm formation. An infarct was considered acute when it appeared to be less than one month old according to the criteria of Mallory[14] and healed when it appeared to be older than one month.

4. *Comparative Frequency of Other Vascular Sequelae.* The frequency of death from vascular phenomena other than coronary thrombosis and/or myocardial infarction, in cases in which the latter was present and healed, was compared in the two groups, as well as the incidence of death from nonvascular causes.

RESULTS

Frequency of Sequelae in the Aorta. There were sixty-seven arteriosclerotic aneurysms in the nondiabetic population, a frequency of 2.1 per cent, as compared with

six such cases among the diabetics, an identical incidence. When these figures are corrected for cases below age twenty because no sequelae of vascular disease were encountered before the third decade, the incidence among nondiabetics was 2.5 per cent as compared with 2.3 per cent in the diabetic population.

There were sixteen cases exhibiting atheromatous embolization among the nondiabetics, a frequency of 0.8 per cent when corrected for cases below age twenty. By comparison there were six cases in the diabetic group, an incidence of 2.7 per cent. As reported elsewhere,[16] the most common organs involved in order of frequency were kidney, pancreas, spleen, thyroid and gall bladder. Such emboli to the kidney may produce relatively sudden elevations in blood pressure (Handler).[17] In the pancreas they may give rise to acute pancreatitis.[16] In other organs, however, they may occur without symptoms and constitute an incidental finding at autopsy.

Thus, while the frequency of arteriosclerotic aneurysm was almost identical in the two groups, atheromatous embolization was over three times as frequent among diabetics as among nondiabetics.

Frequency of Hypertension. The data on hypertension are shown in table 2. Hypertension was almost twice as frequent among diabetics as among nondiabetics (67.8 per cent in the former and 36.3 per cent in the latter). Among the nondiabetics 40.1 per cent of all males showed evidence of hypertension as compared with 31.4 per cent of all females; there was no significant sex difference among hypertensive diabetics. The number of diabetics below age fifty was too small to permit an age comparison with nondiabetics, so that this difference in frequency of hypertension is based on patients over age fifty. An attempt was also made to determine the duration of hypertension in the two groups, but the clinical information was largely inadequate for this purpose. The male sex predominance in nondiabetics was present in all age groups except between seventy-one and eighty when it was approximately equal in both sexes. A slight male sex predominance was also present in all age groups in diabetics where numbers permitted such a comparison, again except between seventy-one and eighty.

Frequency of Myocardial Infarction. The data in table 3 present an analysis of hypertensives in both groups as related to coronary thrombosis and/or myocardial infarction. Approximately one-half of the nondiabetic hypertensive males showed this cardiac lesion, and its frequency in this group showed a progressive rise with age. On the other hand, only about one-third of the hypertensive female nondiabetic autopsy population showed coronary thrombosis and/or myocardial infarction; here too, the frequency of this cardiac lesion increased with age, until in the oldest age group it approached the male incidence.

By comparison, in the diabetic group almost three-fourths of the hypertensive males showed coronary thrombosis and/or myocardial infarction, as did almost three-fifths of the hypertensive females. While there was again an increasing incidence of this cardiac lesion with age among diabetic-hypertensive males, there was some variability in females, and males predominated in all age groups where numbers permitted such a comparison.

In the over-all, coronary thrombosis and/or myocardial infarction in hypertensive cases occurred about two and one-half times as frequently in diabetic as in nondiabetic males and about four times as frequently in diabetic as in nondiabetic females. Among nondiabetic hypertensives without this cardiac lesion there appeared to be no sex predominance, while females appeared to predominate among such hypertensive diabetics.

An over-all comparison of the frequency of coronary thrombosis and/or myocardial infarction irrespective of hypertension is shown in table 4. The total number of myocardial infarcts in this study was 748, or 21.6 per cent of the total autopsy population. When correction was made for autopsies in individuals below age twenty where no cases of this cardiac lesion were encountered, the frequency became 25.4 per cent. There were 617 cases of coronary thrombosis and/or myocardial infarction in the nondiabetic group, or a similarly age-corrected incidence of 23.0 per cent, as compared with 131 among the 260 diabetic patients over age twenty, or a frequency of 50.0 per cent. Thus, the over-all frequency among diabetics was over twice that among nondiabetics.

The ratio of males to females among nondiabetics was 1.7 to 1. Corrected for autopsies in individuals below age twenty, the male predominance increased to 1.8 to 1. By comparison, the sex ratio in diabetics was 1.3 to 1 in favor of males; as there were only four cases with diabetes below age twenty, age-correction did not alter this ratio. While the male sex predominance progressively diminished with age among nondiabetics until it disappeared in the oldest age group, males remained predominant through all age groups among the diabetics, although the numbers were small in some of these.

The striking influence of hypertension on the frequency of coronary thrombosis and/or myocardial infarction in the diabetic group is perhaps best exemplified in table 5, which shows a comparison of this cardiac

TABLE 1

Comparative age distribution of diabetics and nondiabetics

Age Group	Nondiabetic				Diabetic				Total			
	Male		Female		Male		Female		Male		Female	
	No.	Per cent	No.	Per cent	No.	Per cent	No.	Per cent	No.	Per cent	No.	Per cent
0-10	306	16.6	177	13.0	0	—	1	0.7	306	15.6	178	11.8
11-20	22	1.2	21	1.5	0	—	3	2.2	22	1.1	24	1.6
21-30	39	2.1	61	4.5	2	1.6	2	1.4	41	2.1	63	4.2
31-40	93	5.0	109	8.0	10	8.0	6	4.3	103	5.2	115	7.7
41-50	201	10.9	168	12.3	9	7.2	12	8.6	210	10.7	180	12.0
51-60	414	22.5	300	22.0	29	23.2	36	25.9	443	22.5	336	22.4
61-70	455	24.7	297	21.8	48	38.4	53	38.1	503	25.6	350	23.2
71-80	245	13.3	170	12.5	26	20.8	19	13.7	271	13.8	189	12.6
80+	67	3.6	61	4.5	1	0.8	7	5.0	68	3.5	68	4.5
Total	1,842		1,364		125		139		1,967		1,503	
Ave. age at death*	58.8		56.7		60.5		60.3					
	57.9				60.4							

*Exclusive of 0-10 groups

TABLE 2

Comparison of frequency of hypertension* in diabetics and nondiabetics

Age Group	Nondiabetic				Diabetic				Total			
	Male		Female		Male		Female		Male		Female	
	No.	Per cent	No.	Per cent	No.	Per cent	No.	Per cent	No.	Per cent	No.	Per cent
0-10	0	—	1	0.6	0	—	0	—	0	—	1	0.1
11-20	0	—	0	—	0	—	0	—	0	—	0	—
21-30	6	15.4	6	9.9	0	—	1	50.0	6	0.3	7	0.4
31-40	25	26.9	11	10.1	6	60	3	50.0	31	1.0	14	0.9
41-50	79	39.3	39	23.2	4	44.4	9	75.0	83	4.2	48	3.2
51-60	198	47.8	100	33.3	20	68.9	24	66.6	218	11.1	124	8.3
61-70	259	56.9	141	47.5	36	75.0	36	67.9	295	15.0	177	11.8
71-80	135	55.1	95	55.9	19	73.0	14	73.7	154	7.8	109	7.2
80+	37	55.2	31	50.8	1	100.0	6	85.7	38	14.2	37	2.5
Total	739	40.1	424	31.4	86	68.8	93	66.9	825	41.9	517	34.4
Grand total	1,163 (36.3%)				179 (67.8%)				1,342 (38.7%)			

*As evidenced by cardiomegaly in the absence of valvular disease.

TABLE 3

Comparison of age and sex distribution of hypertension* in diabetics and nondiabetics as related to myocardial infarction

Age Group	Nondiabetic								Diabetic							
	Infarct				Non-infarct				Infarct				Non-infarct			
	Male		Female		Male		Female		Male		Female		Male		Female	
	No.	Per cent	No.	Per cent	No.	Per cent	No.	Per cent	No.	Per cent	No.	Per cent	No.	Per cent	No.	Per cent
0-10	0	—	0	—	0	—	1	0.6	0	—	0	—	0	—	0	—
11-20	0	—	0	—	0	—	0	—	0	—	0	—	0	—	0	—
21-30	1	2.6	0	—	5	12.8	6	9.9	0	—	0	—	0	—	1	50.0
31-40	6	6.5	2	1.8	19	20.4	9	8.3	2	20.0	2	33.3	4	40.0	1	16.7
41-50	37	18.4	3	1.8	42	20.9	36	21.4	2	22.2	2	16.7	2	22.2	7	58.3
51-60	104	25.1	27	9.0	94	22.7	73	24.3	15	51.7	17	47.2	5	17.2	7	19.4
61-70	121	26.6	54	18.2	138	30.3	87	29.3	28	58.3	20	37.7	8	16.7	16	30.2
71-80	66	27.0	42	24.7	69	28.1	53	31.2	16	61.5	8	42.1	3	11.5	6	31.6
80+	21	31.3	18	29.5	16	23.9	13	21.3	1	100.0	5	71.4	0	—	1	14.3
Total	356	19.3	146	10.7	383	20.8	278	20.7	64	51.2	54	38.8	22	17.6	39	28.1

*As evidenced by cardiomegaly in the absence of valvular disease.

lesion in nonhypertensives. The over-all frequency in the nonhypertensive, nondiabetic population over age twenty was 4.2 per cent as compared with 5.0 per cent in the nonhypertensive diabetic group covering the same age span. The M/F ratio among nondiabetics was 1.3 to 1, compared with 1 to 1 among diabetics. Because the diabetic group is small, no age-group comparison is warranted.

A comparison as regards age of infarcts is shown in table 6. The frequency of death from an initial acute myocardial infarction is almost identical in the two groups. In the category of healed infarcts only, the incidence in nondiabetics was almost 15 per cent higher than in diabetics, and this relationship was reversed in the category showing both healed and acute infarcts. These data are taken to indicate that while there is no greater tendency among diabetics to succumb to an initial infarct, if recovery occurs the likelihood is considerably greater that the diabetic patient will succumb to a second acute myocardial infarct.

The data in table 7 indicate that the tendency for a diabetic patient to develop myocardial rupture following transmural infarction is over twice as great as in the nondiabetic. Among the diabetics the sex ratio was found to be 1 to 1, while among the nondiabetics females appeared to predominate. Although the number of cases here is too small to warrant a definitive conclusion as regards sex predominance, the findings in nondiabetics are consistent with the reports of others as to sex predominance as well as frequency.[17,15]

TABLE 4

Comparison of myocardial infarcts in diabetics and nondiabetics

Age Group	Nondiabetic				Diabetic				Total			
	Male		Female		Male		Female		Male		Female	
	No.	Per cent	No.	Per cent	No.	Per cent	No.	Per cent	No.	Per cent	No.	Per cent
0-10	0	—	0	—	0	—	0	—	0	—	0	—
11-20	0	—	0	—	0	—	0	—	0	—	0	—
21-30	1	3.6	1	1.6	0	—	0	—	1	2.4	1	1.6
31-40	8	1.2	3	2.8	2	20.0	2	33.3	10	9.7	5	4.3
41-50	46	22.9	6	3.6	2	22.2	2	16.7	48	22.9	8	4.4
51-60	125	30.2	42	14.0	17	58.6	17	47.2	142	32.1	59	17.6
61-70	145	32.1	61	20.5	30	62.5	26	49.1	175	34.8	87	24.9
71-80	80	32.7	51	30.0	18	69.2	9	47.4	98	36.2	60	31.2
80 +	24	35.8	24	39.3	1	100.0	5	71.4	25	36.7	29	42.6
Total	429	23.3	188	13.8	70	56.0	61	43.9	499	25.4	249	16.6
Sex ratio (M/F)	1.7:1				1.3:1				1.5:1			
Ave. age at death*	62.3		67.3		64.1		64.1					
	64.0				64.1							

*Exclusive of 0-20 groups

TABLE 5

Frequency of myocardial infarction in nonhypertensive patients

Age Group	Nondiabetic				Diabetic				Total			
	Male		Female		Male		Female		Male		Female	
	No.	Per cent	No.	Per cent	No.	Per cent	No.	Per cent	No.	Per cent	No.	Per cent
0-10	0	—	0	—	0	—	0	—	0	—	0	—
11-20	0	—	0	—	0	—	0	—	0	—	0	—
21-30	0	—	1	1.6	0	—	0	—	0	—	1	1.6
31-40	2	2.2	1	0.9	0	—	0	—	2	1.9	1	0.9
41-50	9	4.5	3	1.8	0	—	0	—	9	4.3	3	1.7
51-60	21	5.1	15	5.0	2	6.9	0	—	23	5.2	15	4.4
61-70	23	5.1	7	2.4	2	4.2	6	11.3	25	4.9	13	3.7
71-80	14	5.7	9	5.3	2	8.0	1	5.3	16	5.9	10	5.3
80 +	3	4.5	6	9.8	0	—	0	—	3	4.4	6	8.8
Total	72	3.9	42	3.1	6	4.8	7	5.0	78	4.0	49	3.3
Sex Ratio (M/F)	1.3:1				1.0:1				1.2:1			

TABLE 6

Comparison of age of infarct in diabetics and nondiabetics

Fresh only				Healed only				Fresh and Healed			
Nondiabetic		Diabetic		Nondiabetic		Diabetic		Nondiabetic		Diabetic	
No.	Per cent	No.	Per cent	No.	Per cent	No.	Per cent	No.	Per cent	No.	Per cent
173	27.9	37	27.5	282	45.9	41	31.3	162	26.2	53	40.4

TABLE 7

Comparison of myocardial rupture in diabetics and nondiabetics*

Nondiabetics								Diabetics							
Hypertensive				Nonhypertensive				Hypertensive				Nonhypertensive			
Male		Female		Male		Female		Male		Female		Male		Female	
No.	Per cent*	No.	Per cent*	No.	Per cent*	No.	Per cent*	No.	Per cent*	No.	Per cent*	No.	Per cent*	No.	Per cent*
6	1.7	5	3.4	1	1.4	1	2.4	3	4.7	4	7.4	0	—	0	—
Total	11 (2.2 per cent)			2 (1.7 per cent)				7 (5.8 per cent)							

*Per cent of total infarcts

Also tabulated was the frequency of myocardial aneurysm following healing of a transmural infarct. There were thirty-one such aneurysms among nondiabetics, a frequency of 5.0 per cent, and three among diabetics, an incidence of 2.3 per cent. Here then, the statistical relationship is the reverse of that found with myocardial rupture in that the incidence among nondiabetics is about twice as great as among diabetics.

Comparison of Frequency of Other Vascular Complications. Table 8 contains a tabulation of cases in the two groups in which the myocardial infarct was healed and death was due either to some other vascular complication or to noncardiovascular disease. Slightly less than one-half of the nondiabetic group fell into this category as compared with slightly less than one-third of the diabetics. Interestingly, deaths from cerebrovascular accidents and congestive heart failure were more frequent among nondiabetics with healed myocardial infarcts, while deaths from renal disease were considerably more frequent among diabetics. The numbers in the latter category were, however, too small to warrant a definitive conclusion. The figure in the diabetic group does not represent the total figure for glomerulosclerosis, but only cases with healed myocardial infarcts. Those diabetics who recovered from an initial infarct and did not develop a subsequent one also showed a considerably greater frequency of death from nonvascular causes than did the nondiabetics.

In addition, the over-all frequency of cerebral hemorrhage and infarction was compared in the two groups. Since permission for examination of the cranial contents was granted in only about two-thirds of the autopsies, the figures do not represent the true incidence. However, there was no significant difference in the proportion of such examinations between the two groups, and the comparison therefore seems valid. On this basis there was a 9.9 per cent incidence of cerebrovascular sequelae of arteriosclerosis in the nondiabetic group as compared with 11.9 per cent in the diabetic population.

TABLE 8

Cause of death in healed infarcts only in diabetics and nondiabetics

Cause of death	Nondiabetic		Diabetic	
	Number	Per cent	Number	Per cent
Cerebrovascular accident	45	16.0	5	12.2
Congestive heart failure	154	54.6	14	34.1
Uremia	3	1.1	4	9.8
Noncardiovascular renal	80	28.3	18	43.9
Total	282	45.7	41	31.3

DISCUSSION

The over-all incidence of diabetes in this series of autopsies was 7.6 per cent and is therefore greater than the frequency of 4.8 per cent in the study of Thomas and co-workers[18] and of 2.3 per cent in the older series of Clawson and Bell.[19] In the present series the frequency of diabetes in males was 6.3 per cent and in females 9.2 per cent, while in the study of Clawson and Bell it was 2.2 per cent in men and 5.0 per cent in women. In the series of Thomas[18] it was 3.8 per cent in men and 6.2 per cent in women. Within the diabetic group in this

series 47.3 per cent were males and 52.7 per cent females, and this was almost identical with that reported by Clawson and Bell and comparable to that observed by Warren and LeCompte.[2] On the other hand, the figures of Thomas show 50.7 per cent males and 49.3 per cent females in their series of 379 autopsies on diabetic patients. The predominance of females among diabetics has been shown also in surveys based on living patients. Thus, Marks[20] estimated that 2.1 per cent of the male and 3.8 per cent of the female population of 1946 would become diabetic, and Perrott[21] and associates reported a National Health Survey in which 9,182 diabetics were encountered, of which 64.2 per cent were females.

The average age at death for patients dying over age twenty in this series was 57.9 years for the nondiabetics, 60.4 years for the diabetics. The average age at death of nondiabetic patients with myocardial infarction was 64 years; it was 62.3 years in men and 67.3 years in women. By comparison, the average age at death of diabetics with myocardial infarction was 64.1 years, and it was identical in males and females. There is close agreement between these figures and those obtained by Thomas[13] despite the fact that the latter were on the basis of acute myocardial infarction only, while the present series included healed as well as acute infarcts. The present results are also comparable to those of Warren and LeCompte,[2] who also combined healed and acute infarcts in their data.

In the present series myocardial infarction was found over twice as frequently among diabetics as among nondiabetics; it was over twice as frequent in diabetic as in nondiabetic males, and over three times as frequent in diabetic as in nondiabetic females. The results were thus comparable to those of Clawson and Bell.[19] This is in contrast to the results obtained by Thomas,[18] who found a frequency among diabetics almost five times that in the nondiabetic population. The tendency for the male sex predominance in myocardial infarction to disappear in diabetics was present in all three of these studies. It was also true in the autopsy series of Warren and LeCompte[2] and of Marble.[22]

The relationship of hypertension to the susceptibility of diabetics to myocardial infarction appears particularly important and seems not to have been stressed in previous reports, although the figures in the study of Thomas[13] show a 14 per cent higher incidence of hypertension among diabetics. Hypertension, as indicated by cardiomegaly in the absence of valvular disease, was almost twice as frequent among diabetics as among nondiabetics in the present series. In cases with infarction the difference is even more striking: Diabetic males had hypertension 2.5 times more frequently than nondiabetic males, and among females the ratio was 3 to 1.

Criticism might be raised as regards the criteria for hypertension utilized in this study. In general, there are available three methods: (1) Blood pressure determinations during life, (2) heart weight in the absence of valvular disease, and (3) weight of kidneys. As regards the first, there were unfortunately a great many cases in the present series, particularly among the nondiabetics, in which blood pressures were recorded only on terminal admission; frequently in cases of acute myocardial infarction, patients with hypertrophied hearts exhibited hypotension to shock levels. With respect to the second method, heart weight in excess of the levels utilized herein might occur in nonhypertensive individuals who are unusually large, or in cases of idiopathic cardiomegaly; there were very few instances of either of these, and when detected they were not included among the hypertensives. The weight of the pericardial fat, particularly in obese patients, was also considered as a source of error, and for this reason the lower limit in each sex was increased by 50 gm. over that commonly used. The utilization of renal weight appears to offer greater possibility for error than cardiac weight, since many inflammatory and metabolic diseases of the kidney not associated with hypertension may drastically alter the weight. Thus, while the criteria utilized here are subject to error, they appear to be the best available at the present time.

Certain other observations with regard to hypertension are also noteworthy. In nonhypertensives the frequency of myocardial infarction was about the same in diabetics as in nondiabetics. Whereas in nondiabetics hypertension was more frequent in males than in females, it was about equally frequent in the two sexes in diabetics. About one-half of the nondiabetic males with hypertension showed myocardial infarction as compared with about three-fourths of hypertensive diabetic males, while about one-third of hypertensive nondiabetic females showed infarcts as compared with about three-fifths of the hypertensive diabetic females. In the overall, the M/F ratio among nondiabetics was 1.8 to 1 as compared with 1.3 to 1 among diabetics, but in the absence of hypertension it fell to 1.3 to 1 among nondiabetics and 1 to 1 among diabetics. These data, then, indicate that the diabetic heart is probably more susceptible to the effects of hypertension than the heart of the nondiabetic patient.

As mentioned, it is generally accepted that diabetes tends to equalize the discrepancy in incidence of myocardial infarction between the two sexes, although no

adequate explanation is offered for this phenomenon.[29] This is quite apart from the tendency towards such equalization observed following the menopause in women, also shown in certain of the present data, which has been attributed to altered lipid metabolism in postmenopausal females. However, in addition, our data show a similar sex equalization as regards the frequency of hypertension during this period in both diabetics and nondiabetics. In the absence of hypertension the difference in sex ratio diminishes in nondiabetics and disappears in diabetics. Thus again, the data appear to indicate that the increased susceptibility to coronary heart disease in diabetics may be due, in part, to coexistent hypertension.

Also to be considered is the possibility that the hypertension and diabetes may have a common source of origin. In a study of the incidence of adenomatous hyperplasia of the adrenal cortex, Russi, Blumenthal and Gray[23] observed that this lesion was about five times more frequent in diabetes and in hypertension than in the general population. This almost identical increase in frequency in these two disease states indicates that the adrenal cortex may be capable of producing both diseases more or less concomitantly. This observation is made merely to point out that dysfunction of this organ is capable of producing both of these disease states.

The data obtained to test the thesis that arteriosclerosis of major arteries is intensified in diabetic states is inconclusive. On the one hand, the incidence of arteriosclerotic aneurysms of the aorta and of cerebrovascular sequelae appeared to be no higher among diabetics than among nondiabetics, while on the other, atheromatous embolization was over three times as frequent in the diabetic as in the nondiabetic population.

Certain of the present data suggest another consideration in explaining the increased susceptibility of diabetics to the sequelae of arteriosclerosis. While there was no significant difference in the recovery rate from an initial myocardial infarct between the two groups, nondiabetics had 15 per cent more healed infarcts, while diabetics exhibited a greater frequency of similar magnitude of subsequent acute myocardial infarction from which they succumbed. The nondiabetics who recovered from an initial myocardial infarct showed a greater tendency to succumb to other vascular complications, with the exception of renal insufficiency, where diabetic glomerulosclerosis probably asserted itself. Furthermore, the tendency to develop myocardial rupture during recovery from a transmural infarct was about twice as great among diabetics as among nondiabetics in this series, although the data of Thomas[13] do not corroborate this finding. On the other hand, the development of a myocardial aneurysm following healing of a transmural infarct was about twice as frequent among nondiabetics as among diabetics in this series; other reports have not contained information in this regard.

Such observations suggest involvement of small intramyocardial arteries in the diabetic, which does not occur, or occurs in lesser degree, in the nondiabetic. An obliterative process in such vessels might then serve to impair the development of collateral circulation, and such an event would tend to increase the susceptibility to infarction and death from a second coronary occlusion. It would also tend to impair the healing of an acute infarct, and when the latter is transmural, would serve to increase the susceptibility to myocardial rupture. Wessler and associates[18] have pointed out that myocardial rupture appears to be due to impairment of collateral circulation and fibrous tissue formation. In contrast to the increased susceptibility of diabetics to rupture following transmural infarction is the increased ability of nondiabetics to form scar tissue and prevent rupture. The inverse statistical relationship as regards myocardial rupture and ventricular aneurysm in diabetics and nondiabetics supports the validity of this observation. Aneurysm of the tough fibrous wall occurs only because of the high intracardiac pressure.

A recent report by Saphir and co-workers[24] may indicate the nature of a lesion involving small intramyocardial arteries. The latter study dealt with inflammatory lesions of small intramyocardial arteries in patients under age fifty with coronary heart disease; in this series seven instances were in patients with diabetes. As pointed out, in a recent study dealing with the placenta of diabetic mothers Burstein, Soule and Blumenthal[11] demonstrated an obliterating endarteritis of placental arteries consisting primarily of polysaccharide deposition and endothelial proliferation which appeared to be specific for diabetes.

Warren and LeCompte[2] have suggested that faulty polysaccharide metabolism may constitute an important part of the diabetic process. Several studies dealing with circulating glucosamine blood levels in diabetes tend to support such a view.[25,26] The vascular lesions of diabetic glomerulosclerosis and diabetic retinopathy also appear to involve polysaccharide metabolism, but this has not been extended to a successful study of other organs.

Finally, vascular lesions of small arteries might also explain, at least in part, an enhanced arteriosclerotic process of cognate vessels, since they might constitute a local peripheral resistance against which the latter vessels would have to work. In the aorta, involvement of

vasa vasorum might lead to intensified plaque formation on a basis similar to that found in syphilitic aortitis where increased intimal formation is associated with inflammatory lesions of the intramural vascular supply. The failure to observe an increased susceptibility to cerebrovascular sequelae in diabetics further suggests the importance of local phenomena dependent upon the integrity of small vessels.

SUMMARY

This report consists of a statistical study of the effects of diabetes on the sequelae of arteriosclerosis of the aorta and coronary arteries, based on the findings in 3,470 consecutive autopsies. The principal findings were as follows:

1. The over-all incidence of diabetes was 7.6 per cent. There was a predominance of females in the diabetic group and a predominance of males in the nondiabetic group.

2. Hypertension was almost twice as frequent among diabetics as among nondiabetics. It was more frequent in nondiabetic males than females, and was about equally frequent in the two sexes in diabetics.

3. Myocardial infarction was also about twice as frequent in diabetics as in nondiabetics. In the latter group the M/F sex ratio was 1.8 to 1, compared with 1.3 to 1 among diabetics.

4. About one-half of the hypertensive nondiabetic males as compared with about three-fourths of the hypertensive diabetic males showed myocardial infarction, or an increase in the latter group of about 25 per cent; about one-third of the hypertensive nondiabetic females as compared with about three-fifths of the hypertensive diabetic females showed myocardial infarction, or an increase in the latter group of about 27 per cent.

5. The loss of male predominance to myocardial infarction in older age groups in nondiabetics was associated with an increasing incidence of hypertension among older females and a diminishing difference in the incidence of hypertension between males and females.

6. In nonhypertensives there was no significant difference in the frequency of myocardial infarction between diabetics and nondiabetics. In the nondiabetic group the M/F sex ratio was 1.3 to 1 as compared with 1 to 1 in diabetics.

7. The average age at death for diabetics was 2.5 years greater than for nondiabetics. In the nondiabetic group males lived, on the average, 1.1 years longer than females, while in diabetics there was no significant difference between the two sexes.

8. There was no significant difference between the two groups in the average age at death of patients in whom myocardial infarcts were found. However, in nondiabetics, females lived on the average five years longer than males, while in the diabetic group the average age at death was identical in the two sexes.

9. While there was no significant difference in recovery rate between the two groups from an initial infarct, diabetics showed an almost 15 per cent greater frequency of subsequent acute infarction from which they succumbed.

10. Correspondingly, nondiabetics who recovered from an initial infarct showed a greater tendency to succumb to cerebrovascular sequelae or myocardial failure than diabetics.

11. The frequency of myocardial rupture following transmural infarction was twice as high among diabetics as among nondiabetics, while the reverse was found in the frequency of development of ventricular aneurysm following healing of a transmural infarct.

12. There was no significant difference between the two groups as regards the frequency of development of arteriosclerotic aneurysms or cerebrovascular sequelae. However, the incidence of the phenomenon of atheromatous embolization was over three times as high in diabetics as in nondiabetics.

These data are discussed in relation to the adequacy of collateral circulation in determining certain of these differences and with regard to the occurrence of lesions of small intramyocardial arteries in diabetes, which might impair the potential for developing adequate circulation.

SUMMARIO IN INTERLINGUA

Le Sequellas de Arteriosclerosis del Aorta e del Arterias Coronari in Diabete Mellite: Un Studio Statistic

Iste reporto concerne un studio statistic del effectos de diabete super le sequellas de arteriosclerosis del aorta e del arterias coronari. Le base del studio es le constationes necroptic facite in 3.470 casos consecutive. Le plus importante conclusiones es le sequente:

1. Le incidentia general de diabete esseva 7,6 pro cento. Femininas predominava in le gruppo diabetic, masculos in le gruppo non-diabetic.

2. Hypertension esseva quasi duo vices plus frequente inter diabeticos que inter non-diabeticos. Illo esseva plus frequente in masculos non-diabetic que in femininas non-diabetic. In masculos e femininas del gruppo diabetic su frequentia esseva plus o minus le mesme.

3. Infarcimento myocardial esseva etiam circa duo

vices plus frequente in diabeticos que in non-diabeticos. Inter non-diabeticos le proportion inter masculos e femininas con infarcimento myocardial esseva 1,8 a 1; inter diabeticos, 1,3 a 1.

4. Circa un medietate del hypertensive non-diabeticos (mascule) e circa tres quartos del hypertensive diabeticos (mascule) monstrava infarcimento myocardial. Assi le secunde de iste gruppos, in comparation con le prime, monstrava un augmento de circa 25 pro cento. Circa un tertio del hypertensive non-diabeticas (feminin) e circa tres quintos del hypertensive diabeticas (feminin) monstrava infarcimento myocardial. Assi le secunde de iste gruppos, in comparation con le prime, monstrava un augmento de circa 27 pro cento.

5. Le perdita del predominantia mascule inter le casos de infarcimento myocardial in le plus avantiate gruppos de etate de non-diabeticos esseva associate con un crescente incidentia de hypertension inter femininas de etate plus avantiate e con un decrescente differentia inter nasculos e femininas in le incidentia de hypertension.

6. In non-hypertensivos, il non habeva un differentia significative inter diabeticos e non-diabeticos in le frequentia de infarcimento myocardial. In le gruppo non-diabetic le proportion de masculos a femininas esseva 1,3 a 1; in le gruppo diabetic, 1 a 1.

7. Le etate medie al tempore del morte pro diabeticos esseva 2,5 annos plus grande que pro non-diabeticos. In le gruppo non-diabetic, masculos viveva (como valor medie) 1,1 annos plus longe que femininas. In le gruppo diabetic, il non habeva un grado significative de iste differentia inter le duo sexos.

8. Esseva trovate nulle significative differentia inter le duo gruppos in le valor medie del etate a que patientes con infarcimento myocardial moriva. Tamen, inter le non-diabeticos le femininas viveva (como valor medie) cinque annos plus longe que le masculos, durante que in le gruppo diabetic le etate medie al tempore del morte esseva identic in le duo sexos.

9. Esseva trovate nulle significative differentia inter le duo gruppos in le proportion del restablimentos post infarcimento initial, sed le diabeticos monstrava un elevation de circa 15 pro cento (in comparation con le non-diabeticos) in le incidentia de subsequente infarcimento acute con exito mortal.

10. Correspondentemente, non-diabeticos qui se restabliva ab un infarcimento initial monstrava (in comparation con diabeticos) un plus forte tendentia a succumber a sequellas cerebrovascular o a disfallimento myocardial.

11. Le frequentia de ruptura myocardial post infarcimento transmural esseva duo vices plus alte inter diabeticos que inter non-diabeticos, sed le contrario valeva pro le frequentia del disveloppamento de aneurysma ventricular post curation de infarcimento transmural.

12. Esseva trovate nulle differentia significative inter le duo gruppos quanto al frequentia de aneurysmas arteriosclerotic o de sequellas cerebrovascular. Tamen, le incidentia de embolisation atheromatose esseva plus que tres vices plus alte in diabeticos que in non-diabeticos.

Iste datos es discutite in relation al adequatia del circulation collateral in determinar certes de iste differentias e in relation al occurrentia de lesiones in micre arterias intramyocardial in casos de diabete con le effecto possibile de un obstruction del potential pro le disveloppamento de un adequate circulation collateral.

ACKNOWLEDGMENT

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Modern Medical Research

Medical research consists essentially in deliberately inducing or altering bodily or mental function, directly or indirectly, in individuals or groups, primarily for the advancement of health, science and human welfare. Although use of a procedure or its withholding may directly benefit the person involved, its basic purpose is for elucidation and generalization. Today, research is generally undertaken by a team of scientists, including physicians, who are, of course, the only ones licensed to deal directly with patients. Perhaps the essential difference between research and practice lies in attitude or motive. Bean says that clinical investigators rarely meditate on this split in personality—as investigators, they are guided by divine discontent, which sometimes suppresses the physician. The physician is mainly concerned with the patient's welfare; the investigator, although also responsive to this interest, is bent on solving the scientific problem.

There are other differences, particularly in a research institution or where subjects are healthy volunteers. In research, the relation between the parties is more formal, more explicit; payment may flow from the researcher to the subject, or the subject may be given free medical care during and after the research period; exchange of information between the parties is likely to be more active, recognizing the subject's role as a participant. The degree of understanding and nature of consent must be more firm since there is little possibility of assuming the permission that may be implicit when a patient calls upon a physician expecting regular treatment.

The nature of the research problem further helps to distinguish it from general or special practice. Characteristically, the well developed research plan involves a novel or untried method, the modified use of an established means or deliberate replication of a standard practice under controlled conditions. Subjects are selected whereas patients are accepted. The general practitioner, although not by law required to do so, generally admits all who come and treats their conditions, whether interesting or routine.

The extreme in this differentiation is found in research utilization of healthy persons. The investigator draws on volunteers from among medical students, nurses and prisoners and from among his colleagues for "normals." Physicians do not ordinarily practice on normal people, except perhaps in preventive health consultations.

From "Human Experimentation," by Irving Ladimer, J.D., in *The New England Journal of Medicine*, July 4, 1957, pp. 18-24.

Mortality of Patients with Diabetic Acidosis in a Large City Hospital

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INTRODUCTION

Despite marked improvement in the prevention and treatment of diabetic acidosis, it is estimated that 2 per cent of diabetic patients continue to die during acidosis.[1] During the years 1930 to 1951, reports of decreasing mortality rates appeared, with that of Harwood approaching 1.5 per cent.[2,3] Though the groups studied in these reports were not necessarily drawn from comparable populations, the conclusion is inescapable that survival during diabetic ketosis in general has increased.

Various reasons have been offered to explain this decline in mortality. Unquestionably the employment of larger amounts of insulin, a better understanding of fluid and electrolyte derangements, and the "team" approach, have aided in the management of acidosis. Furthermore, measures such as the use of more efficient antibiotics and improved surgery have benefited the treatment of nonacidotic complications. On the other hand, the lessened mortality could be related also to a decrease in the severity of the admission state.

Ten years ago the mortality of patients with diabetic acidosis at the Cincinnati General Hospital approached 50 per cent. This dismal record prompted one of the authors to institute a program of close observation and elaborate documentation of treatment of each patient admitted with this condition. Over a ten-year period 312 cases were studied. Virtually every patient was seen by at least one of the authors, who advised the ward physicians in the management of the case. During this time there was a decrease in the yearly death rate. In the first five years the mortality was 31.4 per cent whereas in the second five years it had significantly declined to 14.5 per cent (figure 1).

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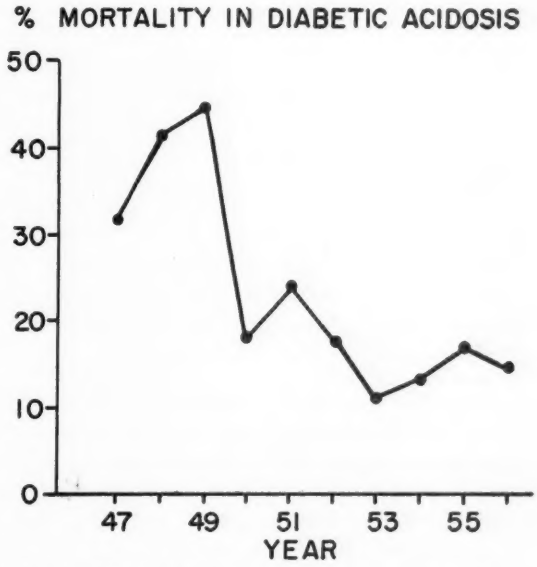

FIG. 1. Mortality in diabetic acidosis in a ten-year period.

This report is an attempt to account for the lessened mortality in a large city hospital population. The findings suggest that though improved management brought about survival in some cases, a decrease in the incidence of nonacidotic complications was equally, if not more, responsible for the decline in mortality.

METHODS

Observations were made on all patients admitted to the Cincinnati General Hospital during the ten-year period 1947-1956 in whom the serum CO_2 content was 14 mM./L. or less due to ketosis, and who lived for at least three hours following institution of insulin therapy. A patient was considered to have survived from acidosis if he was alive thirty days after admission.

Because the mortality was significantly lower in the second half of the time of study, comparisons were made

between the two five-year periods. Data were obtained from each patient concerning his condition at onset of therapy as well as therapy received. One hundred and forty, and 172 patients were observed in the first and second periods, respectively.

An over-all index of severity of each patient was not devised to evaluate his condition at admission. Rather, the individual characteristics, including age, degree of depression of the sensorium, blood pressure, nonacidotic complications, and the concentrations of blood glucose, blood urea nitrogen, and serum CO_2 content were averaged separately for each group. The degree of depression of the sensorium was graded 1 to 4, as follows:

1. Awake.
2. Drowsy, but oriented and responsive.
3. Stuporous. Spontaneous movement or phonation only.
4. Comatose. No spontaneous movement or phonation.

Considerable difficulty was encountered in the evaluation of nonacidotic complications noted at the time of admission. Any system devised to grade these is crude at best, as the actual severity of a complication in a diabetic patient and its effect on insulin action cannot be gauged with accuracy. Nevertheless, complications are so commonly associated with diabetic acidosis that they must be taken into account in any group comparisons. It is likely, however, that many errors in evaluation were nullified because of the large numbers of patients.

The patients were classified in three groups: those without nonacidotic complications on admission, those with moderate, and those with severe nonacidotic complications potentially lethal in themselves. A point system of grading was not used because of the errors in summation of points in a patient with several mild complications. Instead, grouping was made entirely by clinical estimation. Insofar as possible, grouping was also carried out without knowledge of the patient's outcome. This method was believed the most valid for this study inasmuch as almost all patients were followed by one or more of the authors. The nonacidotic complications listed as moderate or severe were as follows:

1. *Moderate nonacidotic complications:* Abscess (thigh, skin, Bartholin's gland, orbit, subungual, rectal, scalp, dental), abortion, acute alcoholism, congestive heart failure without pulmonary edema, hepatic cirrhosis, cerebral thrombosis, epileptiform convulsion, nonsuppurative cholecystitis, gastroenteritis, hemochromatosis without hepatic failure, gross hemoptysis (cause unknown), rheumatic valvulitis, recent morphine administration, myxedema, otitis media, bronchopneumonia, pulmonary infarction, chronic pancreatitis, acute pyelonephritis, acute nonspecific pericarditis, pregnancy, serum sickness, pheochromocytoma, salpingitis, Shigella dysentery, minimal or moderately advanced pulmonary tuberculosis, upper respiratory infection, and Vincent's stomatitis.

2. *Severe nonacidotic complications:* Multiple abscesses of the kidney, anaphylaxis, severe amebic colitis, congestive heart failure with pulmonary edema, cerebral hemorrhage, empyema of the gall bladder, Friedlander's pneumonia, gangrene of an extremity, lateral sinus thrombosis, necrotizing renal papillitis, metastatic carcinoma of the pancreas, myocardial infarction, phlegmonous esophagitis, pneumococcal lobar pneumonia (severe), hemorrhagic pancreatitis, chronic renal failure, basal skull fracture, staphylococcal septicemia, far advanced active pulmonary tuberculosis, thyroid "storm," and hemochromatosis with liver failure and bleeding varices.

Treatment followed a standard regimen sufficiently flexible to meet individual patient needs. Penicillin and Vitamin B complex were given to all patients. The management of nonacidotic complications was believed to be similar in general in the two periods. However, tetracycline drugs were used more frequently in the second period. Studies were made of treatment variables to include the amounts of insulin, glucose, water and electrolytes given in the first six hours of therapy, and of the subsequent administration of norepinephrine and parenteral potassium. It was not believed worth while to estimate therapy other than that with norepinephrine or potassium after six hours because of the deaths or recoveries that occurred between the sixth and eighteenth hours. Methods of analysis of data included the use of the t distribution for making group comparisons, and the use of the chi-square distribution for determining significance of differences between mortalities and between distributions of severities.[4]

RESULTS

In table 1 are listed the admission characteristics related to ketosis of the two groups. There were no significant differences in the mean ages or degrees of depression of the sensorium. Nor was there a difference in the incidence of sustained hypotension not responsive to the administration of fluids or plasma expanders. The mean concentrations of blood urea nitrogen and serum CO_2 content were the same. Though the blood glucose concentration was probably decreased by 49 mg. per cent in the second period ($P<0.05$), this small difference was not believed to be clinically significant. However, it is in the analysis of nonacidotic complications that a significant difference is noted between the two periods.

TABLE 1

The characteristics related to ketosis of the patients on admission, in the five-year periods

Characteristic	1947-1951 (140)	1952-1956 (172)	P
Age* (years)	40.2 (13-72)	42.4 (15-84)	—
Depression of sensorium* (grade)	2.66 (1-4)	2.64 (1-4)	—
Sustained hypotension (number)	15	17	
Blood glucose* (mg.%)	556 (133-1390)	507 (197-1180)	<0.05
Serum CO_2 content* (mM./L.)	8.07 (2.7-14.0)	8.87 (3.5-14.0)	—
Blood urea nitrogen* (mg.%)	29.7 (3-124)	29.6 (4-104)	—

*Data given as mean and range.

In table 2 are listed the distribution of cases according to severity of complications. The distribution in the second period is significantly shifted away from the severely complicated class.

TABLE 2

The distribution of patients with nonacidotic complications between periods

Period	Uncomplicated	Moderately Complicated	Severely Complicated	Total
1947-1951	51 (36%)	62 (44%)	27 (19%)	140
1952-1956	77 (45%)	83 (48%)	12 (7%)	172

x^2=10.9 d.f.=2 P<0.01

In table 3 the treatment given in the first six hours is listed for the two periods. The mean amount of insulin administered in the second period was 64 units greater than in the first period. There were no differences in the quantities of water and sodium given. However, less glucose, amounting to 50 gm. per patient, was given in the second period. Bicarbonate averaging 150 mEq. per patient was given to 116 patients in the second period, in contrast to thirty-two in the first period. The potassium administered parenterally in the first period was not only infrequent but was also less in amount, averaging 35 mEq. per patient in the first period as compared to 49 mEq. per patient in the second period. Norepinephrine for sustained hypotension was not available in the first period but was given to seventeen patients in the second period.

TABLE 3

Parenteral therapy given in the five-year periods

	Therapy	1947-1951 (140)	1952-1956 (172)	P
Mean dose and range in the first six hours	Insulin (units)	392 (100-950)	456 (65-1,200)	<0.01
	Water (liters)	3.01 (1.00-5.00)	3.07 (0.20-6.50)	—
	Sodium (mEq.)	449 (0-450)	417 (0-317)	—
	Glucose (gm.)	142 (0-450)	88 (0-375)	<0.01
Number of patients receiving:	Bicarbonate	32	116	
	Potassium	13	76	
	Norepinephrine	0	17	

The factors believed responsible for death are presented in table 4. It is of interest that in the first period twenty-three of the forty-four who died had demonstrable nonacidotic complications potentially lethal in themselves, whereas nine of the twenty-five who died were similarly afflicted in the second period. However, little significance can be attached to this finding as autopsies were not done on all patients, and the observations are few.

TABLE 4

The incidence of nonacidotic complications in those who died

Complication		1947-1951 (140)	1952-1956 (172)
Infection:			
Pneumonia		5	1
Septicemia		2	1
Necrotizing renal papillitis		2	
Massive skin gangrene		1	
Lateral sinus thrombosis		1	
Amebiasis		1	
Phlegmonous esophagitis			1
	Total	12	3
Vascular:			
Myocardial infarction		3	2
Cerebrovascular accident		2	1
Cardiac failure		2	
Gangrene of leg		1	
	Total	8	3
Miscellaneous:			
Carcinoma of pancreas		1	
Thyroid storm		1	
Skull fracture		1	
Hemochromatosis			1
Acute pancreatitis			1
Uremia			1
	Total	3	3
No demonstrable complication		21	16
	Total Deaths	44	25

DISCUSSION

From the foregoing, it is evident that between the two five-year periods there were differences in the characteristics of the groups as well as the types of therapy carried out. If the mortality rate in the second period had been similar to that of the first, fifty-four deaths would have been expected. Inasmuch as only twenty-five patients succumbed in the latter period, there was a theoretical salvage of approximately twenty-nine cases. Doubtless, the changes both in patient condition and therapy were concerned with the decreased mortality.

With respect to the characteristics of the patients on admission, the significant difference between the periods lay in the distribution of the nonacidotic complications. If the distribution had been the same in the second period as in the first, thirty-three severely complicated cases would have been expected. Since the mortality of this class was very little different between the periods, twenty-six deaths would have been expected instead of the observed nine. Accordingly, it is very likely that a large part of the increased salvage was due to the presence of less severely complicated cases. Undoubtedly the more prevalent use of antibiotics prior to admission eliminated many of the more serious infectious complications.

To evaluate the role of altered management is more difficult. When the severely complicated cases are excluded, there is no significant difference between period mortalities of the uncomplicated and moderately complicated cases either separately or collectively (table 5). Furthermore, if the difference in severity distributions between periods is eliminated by adjusting that of period II to that of period I, and the mortality rates of period II remain unchanged, the resulting mortality of 23 per cent in period II is not significantly different from that of period I. Accordingly, it is not possible to conclude from these observations that change in treatment alone was effective in increasing survival. Nevertheless, it is believed that the use of norepinephrine and massive parenteral potassium was lifesaving in certain instances.

In the first period there were fifteen patients who developed sustained hypotension unresponsive to therapy with ordinary fluids or plasma expanders. Fourteen of these died. In the second period there were seventeen instances of similar hypotension. Norepinephrine was administered in all, with recovery in nine. In four of these cases the amounts employed ranged from 26 to 96 mg. over periods ranging from seventeen to ninety-six hours. The recovery of three of this latter group was believed to be uncontestably related to the norepinephrine therapy.

Parenteral potassium was given infrequently and in small dosage in the first period, with what was believed to be beneficial effect in one patient only. It is certain that many examples of severe potassium deficiency were not recognized at the time. In the second period there were five patients without nonacidotic complications in whom severe or acute potassium deficiencies occurred. Intravenous potassium in amounts ranging from 240 to 480 mEq. were administered up to the thirty-sixth hour of treatment. These large amounts were necessary to correct and prevent the recurrence of respiratory paralysis. It is believed that death would have occurred in the absence of this measure.

SUMMARY

Observations were made on 312 cases of diabetic acidosis in a city hospital during a ten-year period. The mortality decreased in this time from 31.4 per cent in the first five-year period to 14.5 per cent in the second five years. It is suggested that a lower incidence of nonacidotic complications was in large part responsible for the decline in mortality. Though it could not be shown that altered therapy caused increased survival in those without severe complications, the use of norepinephrine and parenteral potassium appeared to be lifesaving in certain instances.

SUMMARIO IN INTERLINGUA

Factores Que Influentia Le Mortalitate De Patientes Con Acidosis Diabetic In Un Grande Hospital Municipal

TABLE 5

The mortality of diabetic acidosis according to severity of nonacidotic complications

Period	Uncomplicated		Moderately Complicated		Severely Complicated	
	Living	Dead	Living	Dead	Living	Dead
1947-1951	41 (80%)	10 (20%)	50 (81%)	12 (19%)	3 (11%)	24 (89%)
1952-1956	69 (90%)	8 (10%)	75 (90%)	8 (10%)	3 (25%)	9 (75%)
	P>0.3		P>0.3		P>0.5	

In le curso de un periodo de dece annos, 312 casos de acidosis diabetic esseva observate in un hospital municipal. Durante le prime periodo de cinque annos, le mortalitate esseva 31,4 pro cento; illo decresceva a 14,5 pro cento durante le secunde periodo de cinque annos. Es suggerite que un reducite incidentia de complicationes non-acidotic esseva in grande parte responsabile pro le reduction del mortalitate. Ben que il non esseva possibile demonstrar que alterationes del therapias habeva causate un augmentate superviventia inter le patientes sin sever complicationes, il pareva que le uso de norepinephrina e de kalium parenteral esseva factores que salvava le vita del patiente in certe casos.

ACKNOWLEDGMENT

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Cholesterol in Diet and Serum

Although it is difficult at the present stage of investigation to measure the effect of cholesterol feeding on human atherosclerosis, A. Keys (*Fed. Proc.* 8:523 (1949); Circulation 5:115 (1952)) and Keys and J. T. Anderson (*Nat. Research Council Pub.* 338 (1954)) have previously reported briefly both survey and experimental evidence indicating that the cholesterol in ordinary human diets has substantially no effect on the concentration of cholesterol in the blood. However, these authors have more recently collaborated with others (Keys, et al., *J. Nutrition* 54:39 (1956)) in an extensive series of dietary experiments on human subjects under very rigidly controlled conditions, and also in both cross-sectional and longitudinal studies on men in Minnesota and Sardinia.

All of the subjects were men between the ages of twenty and sixty and were pronounced to be physically healthy on the basis of medical examinations, including electrocardiography. Subjects in the prolonged controlled experiments were schizophrenic patients in Hastings State Hospital, Minnesota. Men in the longitudinal surveys were professional and business men aged forty-five to fifty-five in 1947 who had cooperated with the laboratory for at least nine years. Surveys on the island of Sardinia included coal miners in the small town of Bacu Abis and moderately active men employed by the city of Cagliari and by the University of Cagliari Medical School.

Dietary cholesterol was computed from food charts. In surveys, except for those where the diets were measured by a U. S. Department of Agriculture group, the dietary intake of cholesterol-containing foods was estimated by individual interviews, with particular attention being given to the intake of eggs, cream, butter, cheese, ice cream, meats, fish and chicken. On the island of Sardinia the individual habits of eating eggs most wholly accounted for the variation in total cholesterol intake. The mean for a total of 187 men was 4.92 eggs per week with the range extending from zero to thirty eggs per week.

Results of six cross sectional surveys on men in Minnesota showed clearly that any relationship between serum cholesterol and that consumed in the diet must be very small. However, it appeared that there is a slight tendency for men who consume the least cholesterol to have concentrations of blood cholesterol slightly lower than the average while those who eat the most cholesterol have the opposite tendency, the deviations in each case being approximately 3 per cent of the mean. Complete independence prevailed over the middle range of intakes, including 60 per cent of the subjects.

Results of the two surveys in Sardinia in 1955, one on moderately active municipal employees in Cagliari and one on poor coal miners in the small mining town of Bacu Abis (representing a two-fold difference in cholesterol intake) failed to show significant differences in serum cholesterol levels.

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Necrotizing Renal Papillitis

Review and Report of a Case Treated by Nephrectomy and Complicated by Waterhouse-Friderichsen Syndrome †

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REVIEW

Eighty years ago Friedreich[1] first described renal papillary necrosis occurring in a seventy-year-old man with obstructive uropathy. Over the ensuing sixty years only seventeen more cases were added, without further elucidation of this clinico-pathological entity until 1937, when Froboese[2] and Gunther[3] first emphasized its frequent association with diabetes mellitus. This association has become more apparent with the increasing reports of more cases. The overwhelming majority of these cases were diagnosed by post-mortem examination.[4] In 1947 Edmondson et al.[5] reviewed the literature and found a total of thirty-three cases, twenty occurring in diabetic and thirteen in nondiabetic persons. These authors added fifty cases of necrotizing papillitis from post-mortem diagnoses in 32,000 autopsies, twenty-nine of these occurring in 859 diabetic patients, and twenty-one in 31,141 nondiabetic patients. All but one of the nondiabetic patients had chronic urinary obstruction.

In 1952 Mandel[6] in his review of the available literature of 160 cases of renal medullary necrosis urged that the diagnosis should be suspected in vivo in patients with diabetes or urinary obstruction in whom there occurs progressive renal insufficiency combined with urinary or systemic bacterial infection. According to an editorial by Mandel,[7] clinical evidence of either diabetes or urinary obstruction was lacking in only 10 per cent of the 180 cases published up to January 1953. In the same year three cases were reported by Silberstein and Paugh,[8] and in 1954 six cases were added by Garrett et al.[9] All of Garrett's cases but one were diabetic females without urinary obstruction. Wall,[10] in discussing pyelographic changes, reported three cases, two of which were diabetics. More recently Whitehouse and Root[11] reported ten cases of necrotizing renal papillitis in the course of 266 post-mortem examinations of 416 diabetic patients who died during a five-year period, and one case diagnosed in a surgically-removed kidney. Thus the total number of cases reported in the literature of necrotizing renal papillitis is now 203 cases over an eighty-year period.

The pathogenesis of necrotizing renal papillitis remains obscure. Pathologically it resembles an ischemic necrosis of renal papillae with concomitant bacterial infection.[11] The usual clinical picture is that of a serious complication of pyelonephritis and is therefore more frequently encountered in patients with diabetes or urinary obstruction, or both.[7]

The necrosis has never been reported to involve the renal cortex. Experimental studies on vinylamine-induced medullary necrosis emphasize the importance of vascular injury and thrombosis as important etiologic factors in renal medullary infarction in the absence of diabetes or urinary obstruction.[12] Vascular congestion in the renal medulla, unlike the situation in the renal cortex, may be equivalent to complete cessation of blood flow with conceivably resultant necrosis if the stasis is of sufficient duration.[13] Upper urinary infection which is of the ascending type in the majority of cases where human medullary necrosis has been reported, may predispose to the development of renal medullary vascular disturbance. The mere existence of pyelonephritis makes the diabetic five to eight times more likely to develop necrotizing papillitis than if it were nonexistent (table 1). Further study on the pathogenesis of necrotizing papillitis is needed.

The following conclusions have been established from clinical and post-mortem data: Necrotizing renal papillitis is more commonly associated with diabetes and urinary obstruction or both. Diabetes was present in 115 out of the 183 cases herein tabulated, an incidence of 62.8 per cent, and the majority of the nondiabetic cases had urinary obstruction. The latter seems to be a more

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*** Winner of the 1956-57 Medical Student-Intern Essay Contest Award for the best review article or case report, sponsored by the American Diabetes Association. This is his prize-winning paper.**

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†The following terms have been used interchangeably: necrotizing papillitis, renal papillary necrosis, renal medullary necrosis, necrotizing pyelonephritis.

TABLE 1

Post-mortem studies on the incidence of pyelonephritis and necrotizing papillitis in the diabetic as compared with the general population

	Autopsies	Type of case	Pyelonephritis		Necrotizing papillitis in the entire series		Cases of necrotizing papillitis in the series having pyelonephritis	
			No.	Per cent	No.	Per cent	No.	Per cent
Ophuls[14] (1926)	3,000	General	123	4				
Edmondson et al.[5] (1924-45)	31,141	General	1,023	3.2	21	0.07	21	2.0
Sharkey & Root[15] (1914-34)	196	Diabetic	35	18				
Baldwin & Root[16] (1934-39)	143	Diabetic	31	22				
Robbins & Tucker[17] (1932-42) as cited by Robbins et al.[4]	307	Diabetic	60	19.5	16	5.2	16	26.6
Edmondson et al.[5] (1924-45)	859	Diabetic	107	12.4	29	3.3	29	27.1
Whitehouse & Root[11] (1950-55)	266	Diabetic			11	4.1		

associated finding in nondiabetic cases (table 2). It is of interest that only nineteen out of 183 cases were free of either diabetes or urinary obstruction. Unilateral involvement has been found in more than one-third of the cases.[6] Two-thirds of the diabetic cases occurred in women, whereas among nondiabetics the men outnumbered the women six to one.[5,6,9,11] The majority of diabetic and nondiabetic cases were over fifty years of age.

Necrotizing papillitis may be present as a subacute type, characterized by pyelonephritis of several weeks' or months', duration with acute exacerbations, or as an acute fulminating disease characterized by overwhelming sepsis and circulatory collapse.[11] A co-existent or resultant adrenal insufficiency has been mentioned in only one case in the literature.[18]

We will present a patient in whom the diagnosis of unilateral necrotizing papillitis was made clinically, subsequently treated by nephrectomy, and yet the patient went on to develop acute circulatory collapse with fatal septicemia and a picture not unlike that of a Waterhouse-Friderichsen syndrome.

TABLE 2

Necrotizing papillitis (183 cases) as it has occurred in diabetes, urinary obstruction, a combination of both, or in their absence

	Cases	Diabetics	Urinary obstruction with diabetes	Non-diabetics	Urinary obstruction without diabetes	Non-diabetic, nonobstructed
Mandel[6] (Review 1952)	160	96	15	64	48	16
Silberstein & Paugh[8] (1953)	3	1	0	2	0	2
Wall[10] (1954)	3	2	0	1	0	1
Garrett et al.[9] (1954)	6	5	0	1	1	0
Whitehouse & Root[11] (1956)	11	11	2	0	0	0
Total	183	115 (62.8 per cent)	17	68 (37.2 per cent)	49 (26.8 per cent)	19 (10.4 per cent)

CASE REPORT

A fifty-nine-year-old white woman was admitted to the Joslin Service of the New England Deaconess Hospital on Oct. 13, 1956. The patient entered the hospital for regulation of recently discovered diabetes mellitus. For about three months prior to admission, patient noted polyuria, polyphagia, polydypsia, and weakness with a ten-lb. unexplained weight loss. Six weeks prior to entry glycosuria was discovered, and the patient was referred to the Joslin Clinic for regulation of diabetes. Past history was not remarkable and system review was otherwise noncontributory.

Physical examination on admission revealed a well-developed, moderately obese, middle-aged woman in no apparent distress. Temperature 99°F., pulse 80, respirations 20, blood pressure 160/80. Important physical findings were as follows: moderately sclerotic vessels in fundi, but no exudates or hemorrhages; grade 2 cardiac apical systolic murmur; the liver was palpable 2 cm. below right costal margin; no costovertebral angle tenderness; moderate cystocoele and rectocoele; absent pedal pulses, slightly edematous but warm feet; no evidence of diabetic neuropathy; skin slightly wrinkled, otherwise not remarkable. The clinical impression on admission was diabetes mellitus.

The patient was brought into good control, with only occasional insulin reactions, and at no time was there any evidence of acidosis. On the third hospital day the patient suddenly experienced a chilly sensation, and the temperature rose to 104°F. Physical examination was unchanged. Blood and urine cultures were obtained, and the urine sediment showed at this time an increased number of white cells and renal epithelial cells as compared with the specimen obtained on admission. On the fifth hospital day the patient complained of mild dysuria and distress in the right flank where tenderness was elicited. Vigorous antibiotic therapy was instituted according to sensitivity studies on the E. coli which grew in both urine and blood cultures. On the tenth hospital day the diagnosis of necrotizing

papillitis was established by microscopic examination of small pieces of tissue that the patient passed via the urine after an episode of increased dysuria. Cystoscopy was performed and a large amount of necrotic material was found in the urinary bladder. Similar material was protruding from the right ureteral orifice. A pyelogram of the right kidney showed a ring shadow in one of the calyces indicative of a sequestered papilla (figure 1). The urine specimen from the left kidney was sterile. On the eleventh hospital day the patient underwent a right nephrectomy under general anesthesia without incident. For the first four days the patient was apparently improving, except for anorexia and a few minor insulin reactions. Five days postoperatively the patient suddenly lapsed into coma and shock. The additional diagnosis of adrenal insufficiency was made, and for the next three days the patient was maintained on Levophed and intravenous hydrocortisone. On this regimen she showed initial improvement with maintenance of her blood pressure, pulse and temperature in normal ranges. She awakened and looked much brighter. Eight days postoperatively the patient complained of pain in the left chest and suddenly stopped breathing and died in spite of attempts at resuscitation.

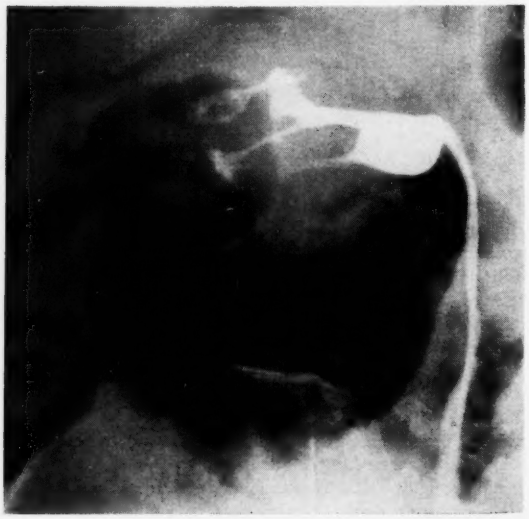

FIG. 1. Retrograde pyelogram of right kidney showing disruption of calyceal architecture, clubbing of middle calyx, and ring shadow in superior calyx characteristic of sequestered papilla. Note gas shadow around inferior pole of the kidney.

Pathologic Observations: The right kidney, surgically removed, weighed 220 gm. The perirenal fat was thickened and indurated with multiple small petechial hemorrhages scattered over its surface. The capsule was stripped with some difficulty. On the inner surface of the capsule there was an exudate with multiple petechial hemorrhages scattered over its visceral surface. On section, two of the papilliform processes in the lower pole showed a purulent soft apex whereas the remainder of the papillary processes were almost entirely absent. Figure 2 shows the microscopic appearance of a necrotic papilla. The pelvis of the kidney was grayish-white and thickened. The superior portion had lost all architectural markings. At autopsy, the operative site was occupied by a blood clot well confined to the bed of the right kidney. The left kidney weighed 240 gm. and showed generally well preserved architecture. A moderate degree of generalized arteriosclerosis was noted. Each adrenal gland (figure 3) was converted to a globular-shaped mass by a large blood clot, about 3 cm. in its greatest diameter in the region of the medulla. The right adrenal weighed 52 gm., left, 63 gm. Histologically (figure 4) there was complete loss of medullary architecture, the central area being occupied by a recent blood clot. The cortex showed only a few areas of well preserved cells. There were numerous small abscesses and extensive areas of necrosis where cortical elements were only recognizable in outline.

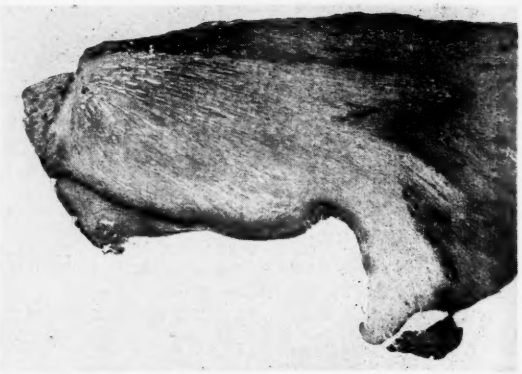

FIG. 2. Microscopic appearance of a necrotic papilla. 10X.

FIG. 3. Gross appearance of both adrenal glands. The medullae are replaced by recent hemorrhage. The cortices are replaced by necrotic elements and small abscesses.

The following is a summary of the final pathological diagnoses. The surgically-removed kidney revealed extensive necrotizing papillitis, whereas the remaining kidney showed mild arteriolar nephrosclerosis. In addition there were septicemia with massive hemorrhage and necrosis in both adrenal glands, multiple lung abscesses, fatty degeneration and periportal in-

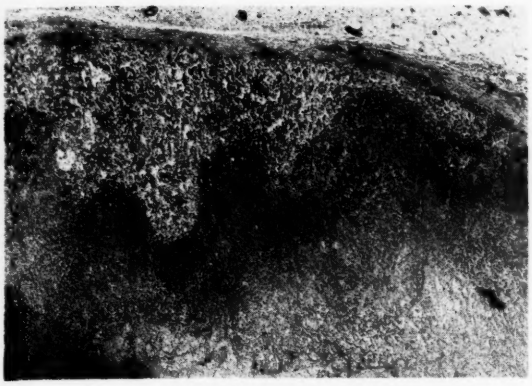

FIG. 4. Microscopic section of adrenal showing extensive areas of hemorrhage, necrosis and abscess formation with only a small amount of recognizable adrenal tissue remaining. 175X.

flammation of the liver, generalized but moderate atherosclerosis, and patchy fibrosis of the myocardium.

DISCUSSION

This patient presented fascinating problems in diagnosis and therapy. The case illustrates an extremely important principle in the management of patients with diabetes mellitus, namely the need for constant awareness of complications in this disease. Sudden fever in a diabetic should direct one's attention to the urinary tract. The urine in this instance contained an increased number of white cells and urine and blood cultures grew E. coli. The colon bacillus has been found to be the most common organism in urinary tract infections of the ascending type in patients with diabetes.[10,19] The suspicion of unilateral renal disease in addition to pyelonephritis led to further diagnostic studies. The pyelographic changes resembled characteristically those described in the literature,[9,10,18] and included displacement of the calyces with deformity and the rare "ring" sign showing the dye around a necrotic papilla. In addition one must always be watchful for any tissue fragments passed in the urine, for they can be invaluable in making the diagnosis. The unilaterality of the disease and the high mortality associated with its presence, and the rarity of pre-mortem diagnosis reported in the literature, all led to the decision for nephrectomy. This was performed with success, and the patient did well for five days postoperatively. Nephrectomy for unilateral necrotizing papillitis has been performed in a diabetic woman who lived two years postoperatively, and subsequently died of underlying diabetic nephropathy in the remaining kidney.[11] In carefully selected patients with overwhelming sepsis from unilateral disease, nephrectomy may be indicated following control of the systemic infection. A hitherto unemphasized complication of sepsis in this disease suddenly ensued, namely circulatory collapse suggestive of acute adrenal insufficiency. The development of Waterhouse-Friderichsen syndrome[20] was a dramatic clinical picture and was the cause of death in this patient in spite of steroid and vasopressor therapy. Only one similar case has been described previously in a forty-six-year-old diabetic woman with E. coli "necrotizing pyelonephritis" who died four hours following nephrostomy.[18] The necrotizing process led to complete destruction of the adrenal glands. In our case the destruction of both adrenals occurred five days postnephrectomy.

What role may an operation play in spreading the sepsis? Since the overwhelming majority of the reported cases have been diagnosed at post mortem,[4] there is at present no definite answer. However, the possible hazard of spreading the sepsis by operation should be weighed against the consequences which occur from a destroyed and functionally useless kidney.

SUMMARY

1. Necrotizing papillitis has been reported in 203 cases in the literature, predominantly in patients over the age of fifty years. The overwhelming majority of the cases have been diagnosed at post-mortem examination.

2. Among the tabulated 183 cases, 115 occurred in diabetics (62.8 per cent). Of the sixty-eight nondiabetic cases (37.2 per cent), forty-nine occurred in patients with urinary obstruction. Only nineteen out of the 183 cases were free of either diabetes or urinary obstruction. The lesion occurred unilaterally in over one-third of the cases.

3. The pathogenesis of necrotizing papillitis remains obscure. Similar lesions have been produced experimentally. Pathologically, it resembles an ischemic necrosis with concomitant bacterial infection. The usual picture is that of a serious complication of pyelonephritis.

4. One case of unilateral acute necrotizing papillitis diagnosed pre-operatively and treated by nephrectomy is herein reported. Five days postoperatively the patient developed fatal adrenal insufficiency. The latter complication has been described only once before in the literature on necrotizing papillitis.

SUMMARIO IN INTERLINGUA

Necrotisante Papillitis Renal: Revista E Reporto De Un Caso In Un Diabetico Tractate Per Nephrectomia E Complicate Per Le Syndrome Waterhouse-Friderichsen

1. Papillitis necrotisante ha essite reportate in 203 casos in le litteratura, predominantemente in patientes

de etates de plus que cinquanta annos. Le vaste majoritate del casos esseva diagnosticate in examines necroptic.

2. Le 183 casos tabulate in le presente articulo include 115 (62,8 pro cento) occurrente in diabeticos. Ex le sexanta-octo casos in non-diabeticos (37,2 pro cento), quaranta-nove occurreva in patientes con obstruction urinari. Solmente dece-nove del total de 183 casos esseva libere de diabete e de obstruction urinari. Le lesion occurreva unilateralmente in plus que un tertio del casos.

3. Le pathogenese de papillitis necrotisante remane obscur. Simile lesiones ha essite producite experimentalmente. Pathologicamente le condition resimila un necrosis ischemic con concomitante infection bacterial. Le usual tableau clinic es illo de un serie complication de pyelonephritis.

4. Es reportate in le presente articulo un caso de acute papillitis necrotisante unilateral que esseva diagnosticate ante le operation e que esseva tractate per nephrectomia. Cinque dies post le operation le patiente disveloppava mortal insufficientia adrenal. Iste complication es describite non plus que un sol vice in le previemente publicate litteratura concernite con papillitis necrotisante.

ACKNOWLEDGMENT

The author wishes to thank Dr. Howard F. Root for permission to report this case and for his invaluable encouragement.

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Essential Fatty Acids and Cholesterol Transport

The relationship of essential fatty acids to cholesterol transport has been demonstrated recently (*Arch. Biochem. Biophys.* 52:180 (1954); Ibid. 57:520 (1955)). Conditions which are accompanied by hypercholesterolemia, such as administration of dietary cholesterol, alloxan diabetes, or hypothyroidism, were found to accelerate essential fatty acid deficiency in rats. We may postulate that if the composition of circulating lipids must remain reasonably constant, the need to transport large amounts of one component of the lipid mixture requires the animal to synthesize or release from his tissues matching quantities of the other components. Thus, any stress that causes increased transport of cholesterol or nonessential fatty acids, or the feeding of large quantities of these components, requires the release of polyunsaturated acids from tissues for incorporation in the cholesteryl esters and phospholipids which are constant components of the plasma lipid. If such a condition persists, the tissues may be depleted of essential fatty acids, the individual may exhibit symptoms of deficiency, and the composition of its plasma lipids may become abnormal. A corollary of this concept is that the requirement for essential fatty acids is relative to the amount of saturated fat in the diet.

Ralph T. Holman, Ph.D., in *Nutrition Reviews*, Vol. 16, No. 2, pp. 34-35.

Determination of Serum Insulin Using the Isolated Rat Diaphragm

The Effect of Serum Dilution

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INTRODUCTION

The method for the determination of serum insulin, based on the stimulation of glucose uptake of the isolated rat diaphragm muscle by small quantities of insulin, has been used by several authors.[1-4] Although the method is relatively easy and reproducible, serious difficulties have been encountered in the effort to make it sufficiently accurate in studies of metabolic problems.

Accuracy is limited by (1) large variations in response of the tissue of different rats to the same dose of insulin and (2) the logarithmic relation between the effect on glucose uptake and the concentration of insulin. From statistical data it has been calculated by Randle[3] that the confidence limits of the determination are about three and one-third times the values found; these figures are in good agreement with our findings recorded below.

Another fact limiting accuracy is that the values reported by different authors for the insulin activity of normal serum vary widely. Vallance-Owen and associates[4] found less than 0.1 milliunits of insulin per ml. of plasma in the fasting state. Randle[3] reported values ranging from 10 to 20 milliunits per ml. in the plasma of healthy individuals, taken two and a half hours after 50 gm. of glucose by mouth. We have reported[2] figures for serum insulin of 0.1 to 3.0 milliunits per ml. while fasting and resting. These differences are far outside the confidence limits mentioned above and hence must be explained in some other way. Differences between plasma and serum, or between fasting and nonfasting subjects, do not seem to be relevant in this respect,[2] so that differences in technic seem to be the most likely explanation at the moment.

Although the technics used by the three above-mentioned authors are basically the same, there are minor differences. One of these is the dilution of serum during the incubation with the diaphragm. Groen and associates[1] and Randle[3] used serum diluted five to ten times with buffer; Vallance-Owen[4] used undiluted serum. It is possible that this variable is responsible for these discrepancies. Therefore, we made systematic investigations of this factor which we report in this paper.

METHODOLOGY

For these experiments the "pooled diaphragm technic" previously described by us[2] was rejected for the following reasons: (1) The effects obtained with concentrations of insulin of 0.1 to 1 milliunits per ml. of incubation medium were sometimes low, possibly because of the damage done to the tissue by dividing the muscle in four or five pieces and by the long time (fifteen minutes) required to collect the tissue from eight rats; (2) the theoretical advantage of pooling diaphragms of several rats often proved to be small in practice since standard deviations remained high; (3) last, but not least, the method required a great number of rats.

The following technic, using single hemidiaphragms, overcomes these difficulties to a certain extent and proved to be reliable within certain limits. It deviates from the old technics as follows:

1. Rats weighing 110±5 gm. were used. Liébecq[5] found that rats of this size show the greatest insulin effect when it is expressed as percentage increase of glucose uptake.

2. The whole diaphragm was carefully and quickly dissected, spread out on a piece of filter paper, blotted slightly to remove fluid, and divided with scissors into two approximately equal pieces.

3. The two hemidiaphragms were incubated, as described previously, in separate flasks containing 1 ml. of

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gassed (93 per cent O_2 + 7 per cent CO_2) buffer solution of 150 mg. per cent glucose. Depending on the object of the experiment both flasks either contained known but different concentrations of insulin, or one flask a known and the other an unknown amount of the hormone.

4. After ninety minutes of incubation, the glucose concentration in the medium was determined by the method of Hagedorn and co-workers.[6]

5. The effect of insulin was expressed as the increase of glucose consumption per hemidiaphragm instead of per 100 mg. wet tissue as described previously.

According to Liébecq[5] the glucose consumption of hemidiaphragms, with or without insulin, is quite independent of the weight of the diaphragms, thin hemidiaphragms of small rats taking up as much glucose as thick hemidiaphragms of heavy rats. Therefore, glucose uptake per gram of incubated tissue, times the weight of the tissue per flask, i.e., the glucose utilization per flask, is essentially constant. We have found that the values for glucose uptake per hemidiaphragm give more consistent results and smaller standard deviations than those calculated on the basis of tissue weight.

Experiments with different known concentrations of insulin showed: (1) A considerable variation in glucose uptake per hemidiaphragm of different rats with the same amount of insulin, as was anticipated; (2) a considerable day-to-day variation in the mean value of the glucose uptake of a group of rats receiving the same dose of insulin; (3) an approximate linear relationship between the logarithm of the insulin concentration and glucose uptake in the range of 0.03 to 8 milliunits of insulin per ml. of incubation medium (see table 1 and figure 1).

On the basis of these findings, the actual test is carried out in a number of parallel experiments by estimating the difference in glucose utilization of the two

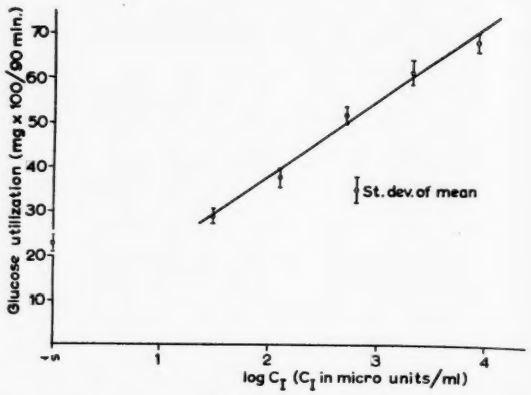

FIG. 1. Standard curve showing approximate linear relationship between glucose utilization (in mg. per half-diaphragm in 90 minutes) times 100 and the logarithm of the insulin concentration (in microunits/ml. incubation medium; 1 microunit=10^{-6} unit).

halves of the same diaphragm. One half is incubated with a known concentration (I_s), the other with the unknown concentration (I_x) of insulin. I_s is always taken in the middle of the linear range.

Assuming the above-mentioned linear relationship between glucose uptake and the logarithm of the insulin concentration, and assuming also that the slope of this linear regression line is the same for all rats and for all days, the mean value of I_x can be calculated by the equation:

$$D_M = \frac{(G_s - G_x)_M}{b} \qquad (1)$$

in which D_M is the mean value of $\log \frac{I_s}{I_x}$

G_s = glucose uptake in medium with I_s

G_x = glucose uptake in medium with I_x

$(G_s - G_x)_M$ = mean value of the difference in glucose uptake in n tests with I_s and I_x

TABLE 1

Mean glucose utilization (mg. glucose x 10^2/90 min.) of hemidiaphragms incubated with different concentrations of insulin (mU/ml. incubation medium)

	Insulin concentration in mU/ml. incubation medium											
Date	0	n	0.03	n	0.125	n	0.5	n	2	n	8	n
6-12-55	14.6	5	20.0	5	27.6	5	48.0	5	61.1	5	67.8	5
12-12-55	34.6	5	35.4	5	41.2	5	56.0	5	71.4	5	65.4	5
4- 1-56	23.0	5	33.4	5	43.4	5	56.0	5	60.0	5	73.0	5
17- 1-56	19.0	5	27.0	5	38.4	5	48.2	5	51.6	5	66.2	5
over-all mean	22.8	20	28.9	20	37.7	20	51.7	20	61.2	20	68.1	20
SEM of over-all mean	2.0		1.7		2.1		1.9		2.7		2.1	

n=number of replicates; $SEM = \sqrt{\frac{\Sigma(x-\bar{x})^2}{n(n-1)}}$

b = slope of regression line (v. figure 1).
The value of b can be obtained by performing the test with two rat diaphragm halves. These are incubated with known but different concentrations of insulin (I_{s1} and I_{s2}) at a fixed ratio, e.g., 4.

$$\text{In this case:} \quad \log \frac{I_{s1}}{I_{s2}} = 0.6$$

$$\text{Accordingly:} \quad b = \frac{(G_{s1}-G_{s2})}{0.6} \qquad (2)$$

The test is repeated over a range of insulin concentrations at the same ratio, i.e., 4. The mean value of b is then calculated by Equation 2.

For any estimated value of D_n of an unknown insulin concentration the confidence limits (D_1 and D_2) can be calculated by the formula:

$$D_{1 \text{ and } 2} = \frac{(G_s-G_x)_m}{b} \pm \frac{t}{b}\sqrt{(a)} \qquad (3)$$

in which:

$$(a) = \frac{(k-1)(sd\Delta G)_s^2+(n-1)(sd\Delta G)_x^2}{(k+n-2)\cdot n} \qquad (4)$$

where: t=Student's t which at F=k+n—2 degrees of freedom has a probability P.
k=number of replicates in test with I_{s1} and I_{s2}.
n=number of replicates in test with I_s and I_x.
$(sd\Delta G)_s$ and $(sd\Delta G)_x$ are standard deviations in k tests with $\frac{I_{s1}}{I_{s2}}$ and n tests with $\frac{I_s}{I_x}$ respectively.

The confidence limits for I_x are therefore

$$T_s \cdot 10^{D_1} \quad \text{and} \quad T_s \cdot 10^{D_2}*$$

The slope b has been determined on several occasions in the course of one year, using the above-mentioned known doses of insulin with a ratio of 4 (D=0.6). While the values of b found in the range 0.125—2 milliunits per ml. were rather constant and in rather good agreement with that obtained from figure 1, those obtained in later times on the lower and higher ends of the regression line were often considerably smaller, indicating a possible curvature on both extremes. We adhered to the described method, however, since the range 0.125—2 was the one most commonly used and the standard used was always 0.5 milliunits/ml. The value for b used was calculated from all the figures of $(G_{s1}-G_{s2})$ obtained in that same range up till the day of the test in question. After some time b tended to become constant at a value of about 18.

Editorial Note: An alternative method for the calculation of the confidence limits of I_x using terminology more familiar to American readers is as follows:

Let R_m=mean value of n tests of $\frac{(I_s)}{(I_x)_m}$

Then the confidence limits $R_{1 \text{ and } 2}$ for given value of Student's t are expressed by the equation:

$$\log R_{1 \text{ and } 2} = \log R_M \pm t \cdot (SEM)_R \qquad (5)$$

where: $(SEM)_R$=standard error of the mean value of log R_m.
But the pooled variance for the calculation of $(SEM)_R$ for k determinations of $\Delta G_s=(G_{s1}-G_{s2})$ and n determinations of $\Delta G_x=(G_s-G_x)$ is:

$$(sd\Delta G)^2 \text{ pooled} = \frac{(k-1)(sd\Delta G)_s^2+(n-1)(sd\Delta G)_x^2}{(k+n-2)}$$

$$\text{Accordingly} \quad (SEM)_R = \frac{1}{b}\sqrt{\frac{(sd\Delta G)^2_{\text{pooled}}}{n}}$$

From Equation (5) the ratio of the confidence limits to R_{mean} is:

$$\frac{R_{1 \text{ and } 2}}{R_{mean}} = \frac{(I_x)}{(I_x)_{mean}} = 10^{\pm t \cdot (SEM)_R}$$

In the example given in the paper t=2 and $(SEM)_R$ =0.25; therefore the ratios of the confidence limits $I_{1 \text{ and } 2}$ to I_m are:

$$\frac{I_{1 \text{ and } 2}}{I_m} = 10^{\pm 0.5} = 3 \text{ and } 1/3$$

(For a discussion of the use of pooled variance in determining confidence limits of a value calculated from two groups of measurements see: Snedecor, George, *Statistical Methods*, chapter 4, Iowa State College Press, Ames, Iowa, 1946.)

Standard deviation $(sd\Delta G)_s$ was rather high: In April 1956 it was 10.6 (k=47); in September 1956 it was 9.6 (k=90) and changed very little afterwards. In nearly every test five animals were used (n=5) and therefore the confidence limits became practically constant, (a) being almost completely determined by k and $(sd\Delta G)_s$. With k=90, n=5, $(sd\Delta G)_s$=10 and $(sd\Delta G)_x$ = about 7, (a) becomes about 20. Taking P=0.05, t is 2.0 (F=93) and therefore $t/b\sqrt{a}$ becomes about 0.5 and the confidence limits $10^{0.5}$=3 and $10^{-0.5}$=1/3. This means that when a certain value I is

*estimates of variance used are

$$SD = \text{standard deviation} = \sqrt{\frac{\Sigma(x-\bar{x})^2}{(n-1)}}$$

$$SEM = \text{standard error of mean} = \sqrt{\frac{\Sigma(x-\bar{x})^2}{n(n-1)}}$$

found for an unknown concentration, the probability is 95 per cent that the true value is between 1/3 I and 3 I.

For the determination of the insulin activity of serum it was diluted to the desired extent by adding calculated amounts of buffer without glucose and/or buffer containing 500 mg. per cent of glucose in such a way that the glucose concentration in the buffer-serum mixture is 150 mg. per cent. The insulin activity of this mixture is tested as described above, using one hemidiaphragm of a rat, and a standard insulin solution in buffer (usually 0.5 mU/ml.) is tested using the other hemidiaphragm. For every determination at least five animals are used. The calculation of the insulin activity in the serum-buffer mixture was carried out as described above. From this the serum insulin concentration per ml. is found by multiplication by the dilution-factor.

The sera used were obtained from normal individuals and patients not suffering from diseases that interfere with carbohydrate metabolism. Blood was taken early in the morning while fasting. Dilutions more than fifty times have not been used because the effect to be measured became too small.

RESULTS

In table 2 and figure 2 the results of these experiments are given. Insulin concentrations found are indicated on the ordinate on a logarithmical scale with their confidence limits for P=0.05.

In all cases the serum insulin values found with high percentages (100 to 50 per cent) of serum are considerably less than those found with smaller percentages (5 to 10 per cent). In most cases the differences between the values obtained with the highest and the smallest serum concentration used were statistically significant, as there was no overlapping of the ranges of probability. In three of the six cases the serum insulin values obtained with nearly undiluted serum were close to those given by Vallance-Owen et al.[4] and all of them were below 1 milliunit/ml.

It seems justified to conclude from these data that the low values for normal serum insulin, recorded by the last-mentioned authors, are at least in part due to the fact that they use undiluted serum for the determination.

As to an explanation for this "dilution phenomenon" at least two possibilities have to be considered. In the first place one could suggest that undiluted serum is an unfavorable, unphysiological medium for the diaphragm tissue and that the high protein concentration causes a diminished ability of the muscle cells to take up glucose. A second explanation would be that the serum contains

TABLE 2

Case	Age	Diagnosis	Per cent serum in incub. med.	Insulin activity (mU/ml.)	Confidence limits (P=0.05)
C	Male	72 Hypertension	50	0.3	0.1 – 0.8
			20	1.2	0.5 – 2.9
			10	1.6	0.7 – 4.1
Z	Male	60 Hypertension	50	0.7	0.3 – 1.5
			20	0.9	0.4 – 2.0
			10	4.0	1.8 – 9.0
Ha	Male	48 Ulcus jejuni	70	0.9	0.4 – 2.1
			20	2.5	1.1 – 6.0
			10	4.6	2.0 –10.8
			5	3.1	1.4 – 7.3
			2	3.4	1.5 – 7.9
Ho	Male	64 M. Bechterew	90	0.1	0.04– 0.3
			10	1.3	0.5 – 3.6
			2	2.3	0.8 – 6.4
R	Male	27 Empyema pleurae	50	0.4	0.15– 1.1
			10	1.4	0.5 – 3.9
			2	3.4	1.2 – 9.5
Ru	Male	33 normal	85	0.1	0.03– 0.3
			10	0.9	0.3 – 2.7
			5	1.1	0.35– 3.3
			2	0.4	0.1 – 1.2

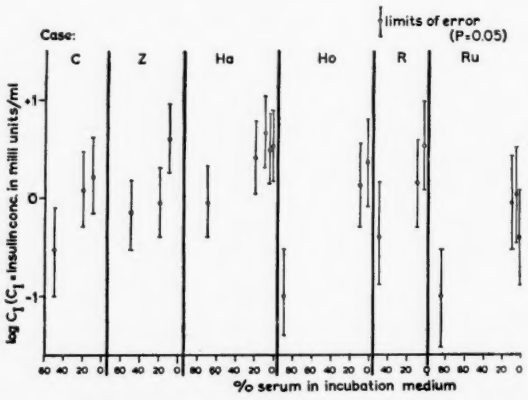

FIG. 2. This figure shows variation in serum insulin values found with different dilutions of serum. On the horizontal: percentage of serum in the medium used for the incubation of the diaphragm tissue; on the ordinate (on a logarithmical scale): serum insulin values found in milliunits per ml. of serum with confidence limits for P = 0.05.

substances counteracting the effect of the serum insulin, and that the activity of these inhibiting substances diminishes more rapidly with dilution than the effect of the serum insulin.

We have found no evidence in favor of the first assumption. On the contrary, we have observed that the effect of pure insulin is not diminished by addition of relatively high concentrations of pure serum albumin.

TABLE 3

Influence of serum albumin* on effect of insulin in the rat diaphragm test

Medium	Albumin %	Insulin mU/ml.	Glucose ut. mg. x 10^2 90 min.	n	Effect of albumin	SEM (1)	P	
1) Buffer	–	–	25.8	8	–	–	–	
2) Buffer	3.5	–	34.4	8	+8.6	2.1	P 1.2	<0.01 >0.001
3) Buffer	–	0.5	56.8	9	–	–	–	
4) Buffer	3.5	0.5	62.0	9	+5.2	4.7	P 3.4	>0.10

* 1.25 gm. of serum albumin (Fraction V acc. Cohn) dissolved in 25 ml. of oxygen-free buffer (Gey and Gey) *p*H 7, containing 100 mg. per cent glucose, was dialyzed in Visking cellophane first for two days with agitation at 0° C. against 2l of the same buffer containing in addition 250 mg. per cent of cystein, and afterwards for another two days under the same conditions against the same buffer solution but without cystein and with 150 mg. per cent of glucose. The final solution (±35 ml.) containing about 3.5 per cent of albumin was used for the experiment.

(1) $SEM=\sqrt{\frac{\Sigma(x-\bar{x})^2}{n(n-1)}}$

In table 3 the results of some experiments of this kind are recorded. A solution of 5 per cent human serum albumin (fraction V of Cohn) was purified by dialysis against buffer containing cystein, to inactivate possible traces of insulin, and the solution obtained, containing about 3.5 per cent of protein, was tested against buffer with and without added insulin (0.5 milliunits/ml.). The albumin itself showed a slight positive effect, comparable with about 0.05 milliunit per ml. of insulin, but it had no significant influence on the effect of added insulin.

As to the second possible explanation for the "dilution phenomenon" we have found that the insulin activity of serum is suppressed by the hormones of the adrenal medulla even in very low concentrations and that the degree of this inhibition is indeed dependent on the dilution of the serum. Experiments dealing with this problem will be published in another publication.[7]

DISCUSSION

It is evident that the elucidation of this problem is of more than methodological importance, as it is directly significant for the problem of the level of normal serum insulin. We are inclined to accept the values obtained after dilution as the more likely ones since figure 2 shows that the values obtained tend to become constant at higher dilutions.

The degree of dilution that was originally described by us (1): five to ten times, and which was later also used by Randle, should therefore be standardized to a dilution of ten times, so that the results of different investigators might better be compared.

SUMMARY

A new modification of the rat diaphragm method for the determination of serum insulin is described in which hemidiaphragms of five rats weighing 110±5 gm. are used.

The values found for serum insulin by this method depend on the concentration of serum in the medium during the determination, lower concentrations yielding higher insulin values.

Possible explanations for this phenomenon are discussed.

This finding explains some of the differences in the values for normal serum insulin as found by different authors.

SUMMARIO IN INTERLINGUA

Le Influentia Del Dilution Del Sero Super Le Determination Del Concentration De Insulina In Le Sero Per Medio De Isolate Diaphragmas De Ratto

Es describite un nove modification del utilisation de diaphragmas de ratto in le determination del concentration de insulina in le sero. Le innovation es le uso de hemidiaphragmas ab cinque rattos que pesa 110±5 g.

Le valores pro insulina seral trovate per iste methodo depende del concentration de sero in le medio durante le processo del determination. Plus basse concentrationes de sero resulta in plus alte valores de insulina. Le explicationes possibile de iste phenomena es discutite. Le phenomeno mesme explica certes del differentias inter le valores pro normal concentrationes de insulina in le sero que ha essite reportate per differente autores.

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Fat Absorption in Man

Opportunities for studying fat absorption in man are uncommon since they depend upon an opportunity to examine thoracic duct chyle. M. J. Albrink, W. W. L. Glenn, J. P. Peters, and E. B. Man (*J. Clin. Invest.* 34:1467 (1955)) were able to perform detailed analyses of the lipids of chyle in five patients with thoracic duct fistulas. The emulsified and soluble lipids were analyzed separately, the division being achieved by slow centrifugation. The concentrations of the lipid components of the creamy layer were calculated as the differences of the values obtained from analyses of the lipid concentrations of the whole fluid and the subnatant following centrifugation.

The lipids of chyle were largely present in the emulsified state. Neutral fat comprised the bulk of the particulate matter, but a small, fairly constant concentration of neutral fat of 6.0 to 10.8 milliequivalents per liter was found in the subnatant. Cholesterol and phospholipids were divided between both fractions, and the ratio of free cholesterol to cholesterol ester was similar in both layers.

One patient was studied after periods of fat feeding and fat restriction. Neutral fat in the emulsified layer increased and decreased with the fat content of the diet. This is in agreement with an earlier study of J. P. Peters and E. B. Man (*Metabolism* 2:30 (1953)) in which it was shown that the lipid pattern of chyle from a patient maintained on intravenous feedings resembled that of serum.

Analyses of the creamy layer disclosed little protein; the amount found was within the error of the method of analysis. Thus, the lipids in this layer are probably in their native state. The cholesterol and phospholipids may be assumed to be dissolved in the neutral fat. In the clear subnatant layer the lipids are held in solution by lipoproteins, most probably synthesized by the liver. When fat is withheld from the diet the chyle and serum lipids are alike, due to the hepatic release of lipoproteins.

In the postabsorptive state the subnatant lipids of chyle vary markedly from those of serum. The cholesterol concentration is lower and neutral fat is higher than in plasma. There is considerable evidence suggesting that a cholesterol-phospholipid-protein complex acts to convey lipids to tissue. The lipids of the subnatant fluid thus reflect the lipoprotein complexes as they are formed and the large difference in neutral fat concentration may be attributed to rapid utilization by the peripheral tissues. These findings in man have essentially confirmed the earlier similar hypotheses based upon experimental studies with animals.

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Pathogenesis of Orinase-induced Beta-cell Degranulation

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Although the hypoglycemic action of the sulfonylurea derivatives is well established, controversy exists as to its mechanism of action. Considerable evidence has accumulated suggesting that the pancreatic β cell is the main target of these drugs. This hypothesis is based primarily on observations that these compounds lower the blood sugar level in the normal and in the partially pancreatectomized, but not in the completely depancreatized nor in the severely alloxan diabetic animal.[1] On the other hand, inhibition of hepatic glycogenolytic enzyme systems[2, 3] or of insulin degradation through an action on insulinase[4] has also received some experimental support as possible mechanisms of hypoglycemia.

Morphologically, these drugs have been shown to produce degranulation of the pancreatic β cells of rabbits and rats when administered for prolonged periods.[5, 6, 7, 8] The functional significance of this sulfonylurea-induced degranulation is not clear. Theoretically, the β-cell granules which represent a reserve of stored insulin may be diminished either by decreased production or increased output of insulin by the β cells. Experimentally, it has been shown that in the rat fasting, a high fat diet, or administration of exogenous insulin, causes β-cell degranulation and also reduces the insulin content of the pancreas.[9, 10, 11, 12] In these instances it is assumed that β-cell degranulation is indicative of suppression of insulin formation. On the other hand, hyperglycemia due to glucose administration also causes degranulation of the β cells and diminished pancreatic insulin content.[13, 14, 15] Under the latter circumstances, it is believed that, although insulin synthesis is increased, the rate of liberation of insulin from the pancreas is so high that the amount of stored insulin, as represented by the granules, is reduced. Some workers have interpreted the degranulation of β cells after sulfonylureas as indicative of suppression of insulinogenesis associated with functional rest of β cells, similar to that observed during chronic hypoglycemia induced by insulin administration.[5] The main argument advanced in favor of this theory was that the β-cell degranulation is not observed after very short-term administration of these drugs. However, in both the cortisone-treated rabbit[16] and the growth hormone-treated dog[17] degranulation of β cells, which in both instances is due to increased insulin output, also is not observed within the first forty-eight hours. An additional argument advanced to support the view that Orinase depresses insulinogenesis was that it causes no histochemically demonstrable depletion of pancreatic islet zinc content.[18] However, this conclusion is not warranted, since little is known as to the actual relationship between insulin, zinc, β cell granules and α cells. Furthermore, this finding could be interpreted as disproof of either the suppression or the stimulation hypothesis.

Since the interpretation of the pathogenesis of β-cell degranulation after administration of the sulfonylurea drugs largely concerns the relationship of the degranulation to chronic hypoglycemia, a study was undertaken in rabbits to compare the morphologic changes observed in the pancreatic islets after Orinase and insulin-induced hypoglycemia.

MATERIAL AND METHODS

The study was carried out on forty-two New Zealand white rabbits of either sex weighing from 2,500 to 3,000 gm. The animals were maintained on Purina rabbit chow and water ad libitum, and were divided into three groups: The first group consisted of twenty-one animals; seven received 5 units of NPH insulin subcutaneously twice daily for periods of up to five days; three received 5 units once daily for up to five days, and five were given 5 units of insulin once daily for two days followed by a single dose of 3 units for four to five additional days. The balance received 3 units of NPH insulin daily for seven days. The second group consisted of fifteen rabbits; each was treated with 0.5 gm./kg. of Orinase* intravenously twice daily for up to seven days. The third group, comprising six animals, served as con-

From the Isaac Albert Research Institute of the Jewish Chronic Disease Hospital, Brooklyn, New York.

*Orinase was supplied through the courtesy of Dr. C. J. O'Donovan of The Upjohn Company, Kalamazoo, Michigan.

trols and were given 20 cc. of saline intravenously once or twice daily for one week. In all animals blood for glucose determination was removed from the marginal ear vein just prior to and for four consecutive two-hour intervals after the injection. The animals were sacrificed by air embolization four hours after the last administration of the test materials. Pancreatic tissue was removed immediately and fixed in Zenker-formol solution. Blocks were embedded in paraffin and stained by a modification of the Masson trichrome technic,[19] by the aldehyde fuchsin method with a trichrome counterstain[20] and by the chrome alum hematoxylin technic[21] with Ponceau fuchsin counterstain.[19] The blood sugar determinations were carried out by the Nelson-Somogyi method.[22]

RESULTS

Rabbits treated with 5 units of NPH insulin once or twice daily could only occasionally be maintained for more than three days because death intervened. The remaining insulin-treated animals (group 1) developed significant hypoglycemia equivalent to those treated with Orinase. The blood sugar curves of two representative rabbits are shown in figure 1. Histologically, the control group, receiving only saline injections, showed no change in pancreatic morphology. The pancreas of the Orinase-treated rabbits, in accord with previous observations, frequently displayed marked or complete degranulation of the β cells (figure 2). On the other hand, the rabbits treated with insulin disclosed no reduction in β-cell granulation (figure 3).

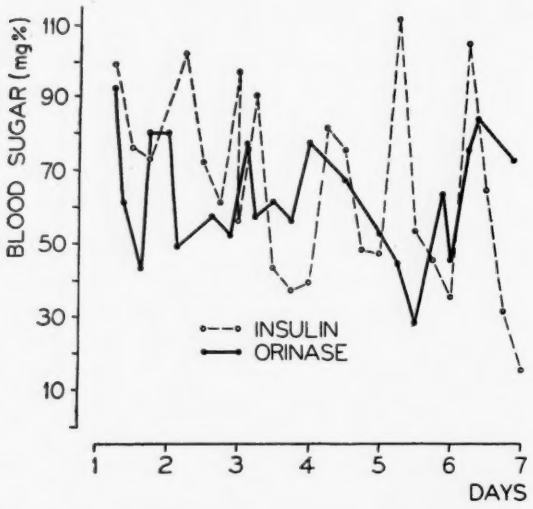

FIG. 1. Representative blood sugar curves of two rabbits, one treated with 0.5 gm./kg. Orinase i.v., b.i.d., the other with 3 units of NPH insulin s. c. once daily.

FIG. 2. Pancreatic islet of rabbit treated for seven days with Orinase showing complete degranulation of the β cells. Aldehyde-fuchsin stain. X 520.

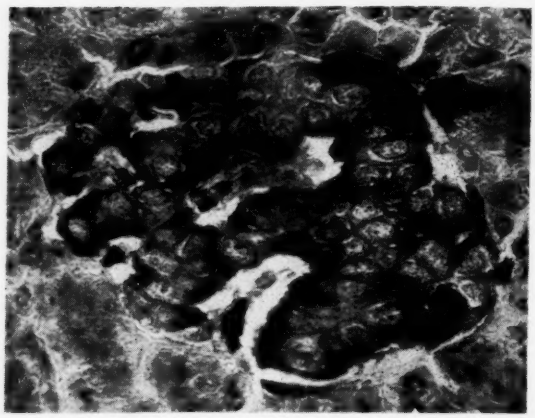

FIG. 3. Pancreatic islet of rabbit treated with 3 units insulin twice daily for seven days. There is normal β cell granulation. Aldehyde-fuchsin stain. X 520.

DISCUSSION

The present study demonstrates that in the rabbit, chronic hypoglycemia of up to seven days' duration, induced by insulin, causes no alteration in the pancreatic morphology whereas Orinase causes degranulation. This lack of effect of exogenous insulin is in certain respects similar to previous observations in the rat in whom β-cell degranulation was not observed after seven days of insulin administration but only after thirty-four to seventy-five days.[11]

The present observations cannot be explained by the point of view that Orinase-induced β-cell degranulation is secondary to extrapancreatically induced hypoglycemia, and suggest rather that insulin output from the pancreas increases under the influence of this drug which is

visualized as β-cell degranulation. It would seem that the β-cell degranulation associated with suppression of insulinogenesis requires a much longer period of hypoglycemia than does that resulting from stimulation of insulin output. Furthermore, the former type of β-cell degranulation apparently occurs less readily in the rabbit than in the rat, since in the rabbit partial or complete starvation causes no change in islet tissue, contrary to what has been reported in the rat.[23]

The hypothesis that Orinase acts through stimulation of insulinogenesis is supported by experiments in which it was shown that, with one exception, normal rabbits and partially pancreatectomized dogs whose β cells have been completely degranulated by steroid and/or growth hormone administration failed to respond with hypoglycemia to a single test dose of Orinase.[24] Because in these animals the pancreas is assumed to be functioning at maximal capacity and there is complete loss of insulinogenic reserve, Orinase is unable to stimulate further insulin release. Similarly it has been shown that a single test dose of Orinase is ineffective in further lowering the blood sugar level of rats after chronic administration of this material.[25]

In addition, in metahypophyseal diabetes a single test dose of Orinase does not cause a decline of the blood sugar,[24] nor does daily administration of the drug ameliorate the diabetic state. Since this type of diabetes is due to insulin deficiency these observations support the viewpoint that Orinase acts through increasing pancreatic insulinogenesis. The ineffectiveness of Orinase under these circumstances is in agreement with similar observations in other forms of insulin-deficiency diabetes induced by pancreatectomy or by alloxan administration.[1] Moreover, after the administration of sulfonylureas the insulin content of the pancreas is diminished[26, 27] and increased amounts of insulin are present in the pancreatic vein blood of dogs[28] and in the plasma of rats.[8] Although this evidence in favor of stimulation of insulinogenesis is rather conclusive, there are other observations[2–4, 29–34] which indicate that there may also be extrapancreatic effects of these drugs that influence the blood sugar. These include particularly some reports of a hypoglycemic effect of Orinase in the absence of the pancreas[29] and also a hyperglycemic effect when the drug is administered rapidly intravenously.[24, 34]

SUMMARY

A study was undertaken to examine in rabbits whether Orinase-induced degranulation of the pancreatic β cells is a primary effect of the drug or whether it is secondary to the sulfonylurea-induced hypoglycemia. For this purpose the pancreatic morphology after Orinase administration was compared with that after equivalent hypoglycemia induced by insulin. It was observed that in the rabbit chronic insulin hypoglycemia of seven days' duration caused no alteration in the pancreatic islets, while Orinase frequently produced extensive or complete β-cell degranulation.

These experiments suggest that the degranulation of β cells induced by Orinase signifies an increase of insulin output from the pancreas which, in turn, accounts for Orinase-induced hypoglycemia. The opposing point of view, that the pancreatic β-cell degranulation is secondary to extrapancreatically induced hypoglycemia, is negated by the fact that the hypoglycemia induced by administration of exogenous insulin for seven days is not accompanied by degranulation.

SUMMARIO IN INTERLINGUA

Studios Relative Al Pathogenese De Disgranulation De Cellulas Beta, Inducite Per Orinase

Esseva effectuate un studio pro determinar in conilios si le disgranulation inducite per Orinase in le cellulas beta del pancreas es un effecto primari del droga o si illo es secundari al hypoglycemia inducite per sulfonylurea. Pro iste objectivo, le morphologia pancreatic post administration de Orinase esseva comparate con illo post equivalente grados de hypoglycemia inducite per insulina. Esseva constatate que in conilios chronic hypoglycemia insulinic de un duration de septe dies causava nulle alteration in le insulas pancreatic, durante que Orinase produceva frequentemente extense o complete disgranulation del cellulas beta.

Iste experimentos pare indicar que le disgranulation del cellulas beta que es inducite per Orinase signala un augmento del rendimento de insulina per le pancreas e que iste effecto, de su parte, causa le hypoglycemia que resulta del administration de Orinase. Le conception contrari—i.e. que le disgranulation del cellulas beta del pancreas es un effecto secundari al induction extrapancreatic de hypoglycemia—es dismentite per le facto que le hypoglycemia inducite per le administration de insulina de origine exogene durante un periodo de septe dies non es accompaniate per disgranulation del cellulas beta.

ACKNOWLEDGMENT

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Effects of Prolonged Glucagon Administration in the Cat and Dog

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It has been postulated that glucagon, the hyperglycemic factor of the pancreatic α-cells, plays an important role in the pathogenesis of diabetes mellitus in man.[1,2] This hypothesis suggests that an excessive secretion of glucagon in relation to insulin results in the diabetic state and is based on the finding of an increased α/β-cell ratio in the pancreatic islets of diabetic patients. One reason that the concept remains controversial is that efforts to induce permanent diabetes in the rat and the rabbit with glucagon have been unsuccessful.[3-7] However, these experiments may be considered inconclusive for the following reasons: The rat and the rabbit are relatively insensitive to the hyperglycemic action of glucagon;[8] they also respond poorly to some diabetogenic agents;[9] and the experimental conditions used were perhaps not ideal.[6,10] The purpose of this study was to determine the effects of prolonged glucagon administration by various routes (including the portal vein) in the two species (cat and dog) most sensitive to glucagon[8] and to certain known diabetogenic agents.[9]

METHODS

Experiments were carried out in six cats and seven dogs, all adult animals. Five different glucagon preparations were used: (1) No. 225-20-255* (20 per cent pure†); (2) No. 208-108B-234* (20 per cent pure); (3) No. 208-158B-197* (50 per cent pure); (4) crystalline glucagon‡ (100 per cent pure); and (5) crystalline Zn-glucagon§ (100 per cent pure). Only animals that received glucagon by continuous intraperitoneal infusion (except dog 559) were anesthetized (sodium pentobarbital); all others were conscious during glucagon administration. In the latter animals, glucagon was infused continuously by means of a gravity drip device regulated by an electronic valve, the details of which have been described elsewhere.[12] This apparatus permits continuous infusion in the conscious, unrestrained animal for prolonged periods (weeks to months). Heparin and penicillin were added to the infusion fluid to prevent thrombosis and infection. The animals' diet consisted of canned dog food (Pard) ad libitum and 20 gm. of sucrose two or three times daily. They were housed in metabolic cages for the collection of twenty-four-hour urine specimens. The doses of glucagon and the routes of administration are given in table 1. One cat (No. 4) and one dog (No. 658) were studied before and after partial pancreatectomy.

Blood sugar determinations were done by the Nelson modification of the Somogyi method.[13] Twenty-four-hour urine glucose was estimated by Benedict's quantitative method.[14]

RESULTS

In preliminary experiments, the hyperglycemic effect of glucagon (20 per cent pure) in various vehicles (water, peanut oil, cottonseed oil, and 15 per cent gelatin) given by three different routes (intramuscular, intravenous and intraperitoneal) was tested by means of a single injection or a five- to seven-hour continuous infusion. Of these methods only the aqueous preparations given intravenously or intraperitoneally by continuous infusion resulted in sustained hyperglycemia (220±60 mg. per cent) throughout the infusion period. All others gave only brief or insignificant blood sugar elevations. The Zn-glucagon suspension produced sustained but less marked hyperglycemia for three to five hours following a single intramuscular injection.

Both aqueous and Zn-glucagon preparations were, accordingly, administered for prolonged periods. Table 1

From the Radioisotope Service of the Veterans Administration Hospital and the Department of Medicine, University of Colorado School of Medicine, Denver, Colorado.

*Kindly supplied by Dr. O. K. Behrens, Eli Lilly and Company, Indianapolis.

†All purity figures are expressed in relation to the activity of the crystalline glucagon standard, which is designated 100 per cent pure.

‡Prepared from an amorphorus preparation supplied by Eli Lilly and Company, Indianapolis, by the method of Staub et al.[11]

§Prepared by Dr. A. Staub.

TABLE 1

Effect of prolonged glucagon administration in adult cats and dogs

Animal no.	Glucagon preparation (purity) per cent	Dose of glucagon preparation per 24 hours (mg.)	Method of administration	Route of administration	Duration of administration (days)	Effect on blood sugar	24 hr. urine sugar (gm.)	Remarks
Cat 11	20	0.5	Single inj. 3x/day	Intraperitoneal	8	Not measured	Slight incr.	Urine glucose returned to control levels when glucagon was stopped.
Cat 15	20	3.0	Single inj. 3x/day	Intraperitoneal	30	Not measured	Slight initial incr.	Urine glucose returned to control levels in spite of continued glucagon administration.
Cat 2	20	6.0	Single inj. 3x/day	Intraperitoneal	46	Hyperglycemia for 1-3 hrs. after each inj.: 145-196 mg.%	0-0.8	Blood and urine glucose values returned to control levels when glucagon was stopped.
Cat 3	20	3.0-5.0	Single inj. 2x/day	Intraperitoneal	108	Hyperglycemia for 1-3 hrs. after each inj.: 163-310 mg.%	0-2.0	Blood and urine glucose values returned to control levels when glucagon was stopped.
Cat 4	20	4.0-5.0	Cont. inf. for 5-7 hrs./day 5 days/wk.	Intraperitoneal	44 before pancreat. 13 after pancreat.	Hyperglycemia maintained during inf.: 155-252 mg.%	0.5-5.0	No change in response to glucagon after partial (50%) pancreatectomy. Blood and urine glucose values returned to control levels when glucagon was stopped.
Cat 5	20	4.0-5.0	Cont. inf. for 5-7 hrs./day 5 days/wk.	Intraperitoneal	13	Hyperglycemia maintained during inf.: 150-286 mg.%	0.5-3.0	Blood and urine glucose returned to control levels when glucagon was stopped.
Dog 378	20	5.0	Cont. inf. for 5-7 hrs./day 5 days/wk.	Intraperitoneal	5	Not measured	0	Urine glucose returned to control levels when glucagon was stopped.
Dog 478	50	5.0-15.0	Cont. 24-hr. inf.	Portal vein	27	Not measured	0-0.5	Urine glucose returned to control levels when glucagon was stopped.
Dog 503	50	11.0-18.0	Cont. 24-hr. inf.	Portal vein	9	Not measured	0.5-1.0	Urine glucose returned to control levels when glucagon was stopped.
Dog 505	50	10.0-15.0	Cont. 24-hr. inf.	Ext. jugular vein	9	Not measured	0.5-2.5	Urine glucose returned to control levels when glucagon was stopped.
Dog 559	50	10.0-15.0	Cont. 24-hr. inf.	Intraperitoneal	8	Not measured	0.5-2.0	Experiment terminated due to repeated clogging of catheter. Urine glucose changes only during glucagon administration.
Dog 658	100	0.4	Cont. 24-hr. inf.	Inferior vena cava	1st exp. 23 2nd exp. 21 (7 wks. later)	Not measured	0-0.5	75% of pancreas removed 2 mos. before first experiment. Urine glucose changes only during glucagon administration.
Dog 781	100 (Zn glucagon)	1.0	Single inj. 2x/day	Intramuscular	14	Not measured	0-0.5	Urine glucose changes only during glucagon administration.

summarizes the data of these experiments. It is noteworthy that although it was possible to maintain hyperglycemia and glycosuria in the cat for periods up to seven hours with constant intraperitoneal infusion of glucagon day after day, in no case did these persist after glucagon was stopped. In the dog, only minimal and transient glycosuria occurred despite continuous and prolonged glucagon administration. No toxic effects or weight loss occurred in any of the animals.

DISCUSSION

The experiments reported here suggest that large doses of glucagon are incapable of causing persistent hyperglycemia and glycosuria in the two species most sensitive to glucagon and certain known diabetogenic agents. Thus, they lend no support to the concept that glucagon is capable of producing permanent diabetes.

The following reports are consistent with the hypothesis that glucagon is involved in the pathogenesis of diabetes. Pituitary growth hormone, which is diabetogenic, has been reported to produce an increased α/β cell ratio,[15,16] and an increased α-cell activity.[16,17] The pancreatic venous blood (but not femoral vein blood) of animals treated with pituitary growth hormone has been found to contain a hyperglycemic substance(s).[18] Hypophysectomy, which ameliorates the diabetic state, has been reported to result in a decreased number of α-cells.[15,16] Glucagon has been reported to inhibit the action of insulin in the isolated rat diaphragm.[19,20] However, there are conflicting observations on each of the reports cited. Using more specific staining technics, Gomori[21] observed a normal α/β cell ratio in a high percentage of diabetics, and Seifert[22] reported an increased α/β ratio in many nondiabetics. The effects of hypophysectomy and pituitary growth hormone on pancreatic α-cells have not been confirmed by recent studies, which employed highly differential staining technics.[23,24] The assumption that the hyperglycemic substance found in the pancreatic vein blood of growth hormone treated animals is glucagon, is rendered questionable by a report that the hyperglycemic effect is eliminated by an adrenergic blocking agent.[25] Finally, there is newer evidence that glucagon does not inhibit glucose uptake in peripheral tissues,[26-28] but actually increases it in the normal and diabetic human.[29-31]

A number of laboratories have studied the effects of prolonged administration of glucagon in the rat and the rabbit. Root[5] administered large doses of glucagon daily for six months to rats intraperitoneally and to rabbits intravenously without producing diabetes or even sustained glycosuria. Ingle et al.[4] gave glucagon by continuous subcutaneous infusion for five days, and by continuous intrajugular infusion for eight days, to normal and partially depancreatized rats and noted only occasional mild glycosuria. Glucagon was found to produce a transient hyperglycemia and glycosuria in the force-fed normal rat, but not in the rat fed ad libitum, even when partially depancreatized.[3] Recently, Salter et al.,[6,7] have reported that glucagon administered intramuscularly caused marked hyperglycemia and glycosuria in force-fed rats. However, in no instance did permanent diabetes develop. The rats became increasingly ill after a few days and only two survived for as long as ten days. Root[5] observed no toxic effects in her rat experiments with doses of glucagon, comparable to those used by Salter et al., administered for six months. In the present studies no toxic effect or weight loss was observed when glucagon in doses up to 18 mg./day was administered for periods up to 108 days.

Salter et al.[6,7] have referred to glucagon as a "diabetogenic agent" and used the term "glucagon diabetes" to describe their findings. Diabetes has been defined as a syndrome characterized by persistent hyperglycemia and glycosuria associated with or resulting from impaired utilization of glucose. If this definition is valid, it seems to us that a distinction should be made between conditions which have been shown to produce this metabolic abnormality permanently (e.g. pancreatectomy, alloxan and pituitary growth hormone), those[9] which induce this state temporarily (e.g. adrenalin and adrenal steroids), and those[9] which produce transient hyperglycemia and glycosuria without impairment of glucose utilization (e.g. force-feeding). Most of the evidence to date appears to be in agreement that glucagon belongs in the third of these categories. Whether this category merits the designation "diabetes" is a debatable issue.

SUMMARY

Experiments in which large doses of glucagon were administered by various routes (including the portal vein) for prolonged periods to thirteen adult cats and dogs are reported. The hyperglycemia and glycosuria induced by glucagon were transient in all animals. The findings are in agreement with previous ones in species (rat and rabbit) which are less sensitive to glucagon and certain known diabetogenic agents than the cat and dog. They lend no support to the hypothesis that glucagon is involved in the pathogenesis of diabetes mellitus.

SUMMARIO IN INTERLINGUA

Effectos De Prolongate Administrationes De Glucagon In Cattos E Canes

Es reportate experimentos in que grande doses de glucagon esseva administrate per varie vias (incluse le vena portal) e durante prolongate periodos de tempore a decetres adulte cattos e canes. Le hyperglycemia e glycosuria inducite per glucagon esseva transiente in omne le animales. Le constatationes es identic con illos previemente facite in species—i.e. rattos e conilios—que es minus sensibile a glucagon e certe cognoscite agentes diabetogene. Esseva trovate nulle supporto pro le hypothese que glucagon participa in le pathogenese de diabete mellite.

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Influence of the World War II Food Shortage on the Incidence of Diabetes Mellitus in Japan

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During World War II and for a few years thereafter, the nutrition of the Japanese people was extremely poor. Death from starvation was not rare, and lesser degrees of malnutrition were commonly encountered. During this period the incidence of diabetes mellitus decreased markedly. This phenomenon, similar to that observed during World War I in Germany by Gottstein and Umber,[5] Singer and Elias,[14] and Beckert,[2] has been reported by many Japanese workers who have considered the cause as deficient caloric intake.[1, 10] Kaito and his co-workers[8] have published statistical studies on the incidence of diabetes mellitus in patients hospitalized in our clinic from 1936 through 1946. In the present report more detailed analytical consideration will be given to the outpatients as well as to the hospitalized cases during 1936 through 1956.

RESULTS

The number of diabetic patients visiting the Third Medical Clinic of Tohoku University Hospital (director, Professor Kurokawa and the late Professor Yamakawa) during the last twenty-one years is depicted in figure 1 and table 1. Also included is the total number of out- and inpatients of this period. During the war years, the number of diabetic patients decreased, reaching a low point during the years 1945 through 1948. The total number of patients, however, remained relatively constant through this period. Rigid government regulation of food supplies was instituted in Japan in 1941. In the Tohoku district (northeastern part of Japan) food shortage became severe first in 1942. After the end of the Pacific War in 1945, food was extremely scarce due to decreased food production and disordered distribution of available food supplies. Food supply improved gradually from 1948 on, and by 1950 was almost normal, although the average food intake of the Japanese did not reach standard caloric requirements until today (table 2). The lowest incidence of diabetes mellitus in our patients was encountered in 1947. In 1951 the number of diabetics abruptly increased, and subsequently the number of diabetic patients continued to rise.

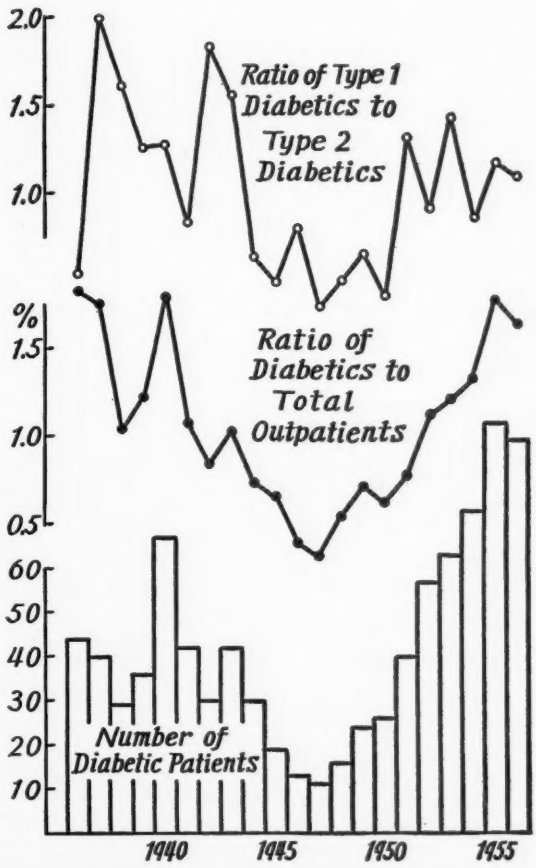

FIG. 1. Fluctuation in number of diabetic patients, ratio of diabetics to total outpatients and ratio of type 1 diabetics (mild and obese) to type 2 diabetics (severe and thin) during 1936 through 1956. Pacific War: Dec. 1941 to Aug. 1945.

It is our practice to divide diabetic patients into two clinical groups. Type 1 diabetes is characteristically mild and, by definition, insulin therapy is not necessary. This

From the Medical Clinic of Prof. T. Kurokawa, Tohoku University School of Medicine, Sendai, Japan.

TABLE 1

Number of diabetic patients in the Third Medical Clinic of Tohoku University Hospital from 1936 through 1956

	Ambulatory					Hospitalized				
	Total patients	Diabetics			Ratio of diabetics to total patients (%)	Total patients	Diabetics			Ratio of type 1 to type 2
		Male	Female	Total			Type 1	Type 2	Total	
1936	2,416	35	9	44	1.82	641	8	15	23	0.53
1937	2,281	26	14	40	1.75	663	12	6	18	2.00
1938	2,781	21	8	29	1.04	727	16	10	26	1.60
1939	2,938	25	11	36	1.22	740	19	15	34	1.26
1940	3,706	49	18	67	1.80	692	23	18	41	1.27
1941	3,882	31	11	42	1.08	651	13	16	29	0.81
1942	3,528	21	9	30	0.85	612	13	7	20	1.85
1943	4,029	34	8	42	1.04	626	11	7	18	1.57
1944	3,965	18	12	30	0.75	678	7	11	18	0.63
1945	2,760	16	3	19	0.68	578	3	6	9	0.50
1946	3,098	13	0	13	0.41	663	4	5	9	0.80
1947	3,312	8	3	11	0.33	604	3	8	11	0.37
1948	2,841	13	3	16	0.56	640	2	4	6	0.50
1949	3,272	12	12	24	0.73	721	9	14	23	0.64
1950	4,031	19	7	26	0.64	813	5	13	18	0.38
1951	5,050	28	12	40	0.79	841	13	10	23	1.30
1952	5,049	37	20	57	1.12	808	18	20	38	0.90
1953	5,202	43	20	63	1.21	795	23	16	39	1.43
1954	5,442	46	27	73	1.34	831	18	21	39	0.85
1955	5,177	67	26	93	1.79	954	26	22	48	1.18
1956	5,416	64	25	89	1.64	889	31	28	59	1.10

TABLE 2

Average nutriment consumption of Japanese people (per man, per day, in urban community). (Reports of the Japanese Welfare Ministry 1956.)

	Cal.	Carbohydrate	Protein	Fat
1946	1,721	—	59.5	16.6
1947	1,857	—	61.6	13.3
1948	1,916	—	64.5	15.5
1949	1,972	—	—	—
1950	2,041	394	71.0	21.0
1951	2,061	398	70.0	21.0
1952	2,042	390	70.6	22.5
1953	2,002	381	69.3	22.4
1954	2,010	381	69.0	23.6
1955	2,025	385	70.0	22.8

Standard requirement of nutriment for Japanese people (man per day) is 2,180 calories and 73 gm. of protein.

type is usually found in older age groups, often in obese patients who are relatively insensitive to insulin. Type 2 diabetes is characteristically severe and, by definition, requires insulin for control. This type of patients is often undernourished and usually sensitive to insulin. The ratio of type 1 to type 2 diabetes is presented in figure 1 and table 1. It can be seen that during the period of reduced incidence of diabetes, a marked reduction in the ratio of type 1 to type 2 took place. During this period the obese and mild diabetics decreased remarkably.

DISCUSSION

A large amount of experimental or clinical work, demonstrating the importance of nutritional factors in the development of diabetes mellitus, has been done. Many investigators (for example, Joslin,[7] Bertram[3]) reported the close relationship between obesity and the onset of human diabetes. Recent studies on the hereditary obesity-diabetes syndrome of mice seem to emphasize the relationship of diabetes mellitus and obesity.[9] Dohan and Lukens[4] produced diabetes mellitus in cats by continuous perfusion of glucose. A similar attempt was made by Yoshikawa[15] in our laboratory. Although these studies show that diabetes can be induced in animals by excessive carbohydrate intake, it is not known whether the same applies also to human subjects. It is well known, however, that obesity or excessive caloric intake has an adverse effect on human diabetes, and in fact, may produce the appearance of the disease in a "latent diabetic" who otherwise would have been unaware of any diabetic tendency.

There may be many factors to account for the decreased incidence of diabetes mellitus during the years 1942 through 1948. For example, disruption of family groups, loss of property, uncertainty as to the future, and poor living conditions could very well influence the incidence and severity of diabetes. The most important factor, however, is felt to be poor nutrition. In view

of a generalized reduction of caloric intake by the population it should be expected that there was a much greater decrease in the mild, obese, "type 1" diabetics whose diabetic symptoms were abolished by food restriction, and only a relatively slight decrease in thin, severe, "type 2" diabetics. Actually, the population of Japan was receiving the pre-insulin era treatment for diabetes during the war years, i.e., a reduction in caloric intake to the point of starvation. Further evidence, showing nutrition as the principle cause for reduced incidence of diabetes during the war years, is the fact that the same phenomenon was observed also in neutral European countries which did not participate in World War II but did experience a definite and often marked reduction in caloric intake. It is of interest that in these countries sugar and fats were two of the most scarce items. Schliack[13] observed in Germany the interesting fact that the number of diabetic patients, which decreased during World II, increased abruptly from 1950, when the fat intake of German people was augmented remarkably without simultaneous increase in carbohydrate intake. The present study and Schliack's report suggest the possibility of prevention of diabetes mellitus by keeping the body from overnutrition or overintake of fat.

Heredity has been shown to be an important "etiological" factor in human diabetes. Other factors are important, however, in determining which of the many individuals having an inherited diabetic tendency will develop clinically apparent disease. Thus, scarcity of food can reduce the incidence of clinical diabetes mellitus, although it would have no permanent curative effect.

To summarize, we feel that the World War II food shortage in Japan favorably affected diabetes mellitus in at least two ways: (1) in known diabetics, the severity of disease was lessened by the prolonged reduction in caloric intake, and (2), the development of clinically apparent diabetes was prevented in many instances, thus leading to lowered incidence of diabetes.

SUMMARY

The incidence of diabetes mellitus in out- and in-patients at the Third Medical Clinic, Tohoku University, was analyzed for the period 1936 through 1956. During the war years, the number of diabetic patients decreased, reaching a low point during the years 1945 through 1948. This decrease was most striking among type 1 diabetics (Type 1 diabetics, by definition, have a mild form of the disease not requiring insulin therapy, are often obese, and are usually in older age groups.) It is concluded that the decreased incidence of diabetes seen in our clinic was due principally to the reduced caloric intake during and after the war years.

SUMMARIO IN INTERLINGUA

Le Carentia De Alimentos In Japon Durante Le Secunde Guerra Mundial E Su Influentia Super Le Incidentia De Diabete Mellite

Le incidentia de diabete mellite inter le patientes externe e interne al Tertie Clinica Medical del Universitate Tohoku esseva analysate pro le periodo ab 1936 usque al fin de 1956. Durante le annos de guerra, le numero del patientes diabetic decresceva, attingente su minimo durante le periodo ab 1945 usque al fin de 1948. Iste reduction esseva le plus frappante inter diabeticos de typo 1 (i.e. diabeticos qui ha le morbo in un leve forma que non require therapia a insulina e qui es frequentemente obese e pertine usualmente a gruppos de etate plus avantiate). Le conclusion es formulate que le reduction del incidentia de diabete observate a Tohoku esseva primarimente le effecto del reducite ingestion caloric durante e post le annos de guerra.

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Response to Alloxan Modified by Partial Pancreatectomy

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When alloxan is injected into animals, one of the effects is a hypoglycemia preceded by a transient elevation of blood sugar and followed by hyperglycemia that is often permanent. Some time before the diabetogenic capacity of alloxan had been discovered, its more immediate hypoglycemic effect was observed by Jacobs[1] in rabbits. The precipitate drop in blood sugar that simulates insulin action, since it occurs at the time of extensive islet necrosis, led many[2-5] to the conclusion that the cause is the liberation of the final remnant of insulin from the dying beta cells of the pancreas. Studies on the alloxan reaction after pancreatectomy in several species have generally supported this postulate, though they have sometimes been equivocal.[6] Furthermore, the albino rat, though usually the first choice for animal experimentation, has been notably absent from this problem because of the difficulties attendant upon pancreatectomy in the species. It was to fill that deficiency in alloxan experimental work that the present study was undertaken.

EXPERIMENTAL

Albino rats were partially depancreatized by a technic essentially as described by Ingle and Griffith.[7] Pre- and postoperative care described by Treadwell and Roe[8] improved survival, which in our hands varied from 55 to 95 per cent depending on the strain of animal and the age at operation. All surgery was performed on rats under Evipal anesthesia and was done throughout the study by one operator (P.J.B.) to avoid variations in operative skill. About 250 partial pancreatectomies were required to obtain enough survivors for the projected tests.

Throughout the study, males and females were used in equal numbers to avoid any confusion of results by the sex factor, which is of major effect in experimental diabetes.[9] The two age groups employed for partial pancreatectomy were thirty- to forty-day-old immature animals and 250- to 350-day-old adults.

The young animals after operation were reared to adulthood and in the sixth postoperative month were given alloxan after an assessment of the damage that surgery had made in their glucose metabolism. In the adult groups the effect of partial pancreatectomy was evaluated at the third or fourth postoperative week, and the alloxan experiments followed shortly thereafter. Albino rats of both the Wistar and the Osborne-Mendel strains were used to permit further comparison of these two hereditary lines, which are known to differ in glucose economy,[10] in their pattern of reaction to alloxan when unoperated,[11] and in the ease with which diabetes may be produced through surgery.[12]

Alloxan monohydrate was administered subcutaneously, following a four-day fast, at a level of 20 mg. per 100 gm. body weight. Fifteen minutes thereafter the animals were returned to their usual Purina Laboratory Chow diet fed ad libitum. To follow the blood sugar changes tail blood was obtained at intervals during the first forty-eight hours after alloxan. Subsequently the diabetic state was assessed by a fasting oral glucose tolerance test two weeks after injection and, at three weeks, by examination of the urine for glucose and acetone bodies and of the postprandial blood sugar. Blood sugars were estimated by the method of Folin and Malmros,[13] urine glucose by Somogyi's quantitative procedure[14] and ketonuria was evaluated qualitatively by a nitroprusside spot test.*

RESULTS

Partial pancreatectomy was found in this study to have essentially the same effect on the blood sugar response to alloxan whether the operation was done before maturity or in adulthood. Furthermore, both sexes were similarly affected, and the presence or absence of pancreatectomy diabetes was of little influence. For these reasons it has been possible to simplify the presentation of results merely to a demonstration of the difference in

From the Biochemical Laboratory, Metropolitan Life Insurance Company, New York City.

*Several companies market this type of simple test. The one used here is manufactured by the Denver Chemical Company, New York, and is sold as Acetone Test-Denco.

blood sugar response between intact and operated animals and between the two animal strains.

Figure 1, which is the pattern blood sugar follows after alloxan in Wistar animals, is marked, in the unoperated subject, by a strong hyperglycemia reaching a peak at twenty-one hours followed by a steep decline to relatively low levels at thirty hours. Animals having been subjected to partial pancreatectomy present, in contrast, a greatly flattened response curve. The initial blood sugar rise is decreased, and the intervening relative hypoglycemia is of less intensity. Each point plotted in the charts represents an average on at least thirty animals. As in earlier studies, wide individual variability was found. However, statistical evaluation confirmed the high significance of this difference, in the Wistar strain, between animals partly deprived of pancreas and their intact controls.

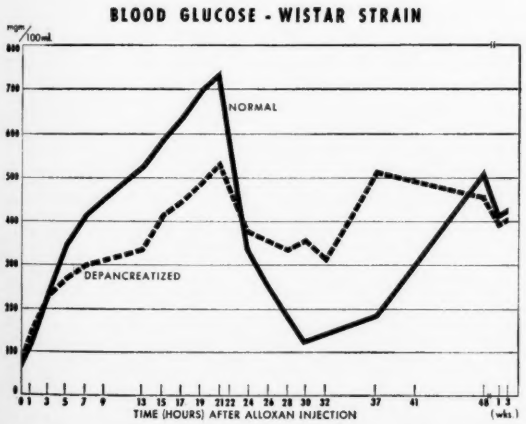
Figure 2 presents a study entirely similar to that in figure 1, except that Osborne-Mendel strain rats were used. Because of a shortage of operated animals, mortality in this strain being particularly severe, observations on blood sugar levels were largely confined to those hours in which significant changes would be most likely to occur. A comparison of the control subjects in the two figures demonstrates the difference in response behavior of the two strains. The Osborne-Mendel animals show a nearly complete lack of triphasic response, and it is, therefore, not surprising that pancreatectomy in this strain is without further influence.

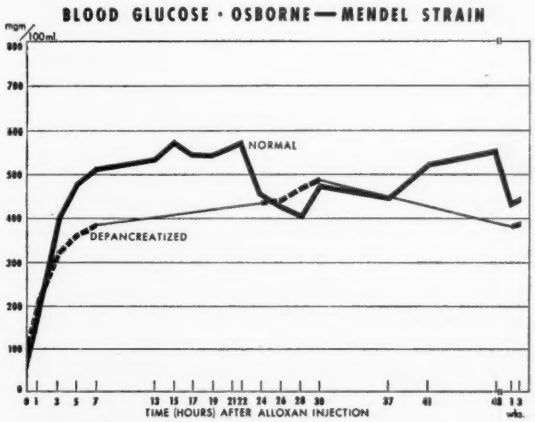
The diabetic condition of the alloxan-treated animals was further assessed by determining the oral glucose tolerance at two weeks and the urinary excretion of glucose and ketone bodies at three weeks after injection. These measurements together with postprandial blood sugar are presented in table 1 for the partially depancreatized animal and its unoperated control in two strains.

Fasting blood sugar values obtained in the glucose tolerance test emphasize the outstanding strain difference in alloxan diabetes. Severely diabetic animals of the Osborne-Mendel strain have a characteristic high fasting blood sugar whereas the Wistar animals are inconsistent in this regard, many developing more or less severe hypoglycemia in fasting. Postprandial blood sugars in the two strains are similar and, of course, elevated.

In the Wistar strain partial pancreatectomy prior to alloxan had an effect on the diabetes induced by alloxan only among the small group depancreatized as adults. Among these animals the fasting blood sugar is greatly depressed so that, as shown by standard deviation, severe hypoglycemia may occur. Subsequent one-half-hour and two-hour values after glucose are correspondingly low. These animals were free of ketonuria when fed. In contrast, the partial pancreatectomy before maturity appears to be without effect.

With the Osborne-Mendel strain the position is reversed. Here adult pancreatectomy made but little change from the control. But partial pancreatectomy at an early age affected the diabetic state after alloxan, so that fasting hyperglycemia and sugar levels during the tolerance test were significantly depressed, postprandial blood





FIGS. 1 & 2. Blood sugar changes in partially depancreatized and in intact animals following alloxan. Alloxan was given to adult rats only but the operation was performed on half the animals in infancy and half of the animals in adulthood. The time of operation had no effect on the subsequent alloxan response. Only animals severely diabetic following alloxan are included in the study. The operation produced no diabetes in the Wistar strain (figure 1); in the Osborne-Mendel strain (figure 2) about 50 per cent of the subjects were already diabetic due to operation before the alloxan was given.

TABLE 1

Blood sugar, glucose tolerance and urine studies on alloxan diabetic rats, with and without preliminary partial pancreatectomy

Animal strain	Time after glucose, hour	Oral Glucose Tolerance* 0	0.5	2	Postprandial† blood sugar mg. per cent	Urine‡ Glucose per cent	Per cent of rats with ketonuria
		Blood glucose mg. per cent					
Wistar	Control, not depancreatized (61)§	134‖ ± 62	266 ± 69	162 ± 72	425 ± 72	6.4 ± 1.8	32
	Adult pancreatectomy (12)	¶76 ± 33	177 ± 66	82 ± 43	427 ± 188	8.0 ± 3.3	none
	Immature pancreatectomy (26)	154 ± 79	269 ± 91	196 ± 97	406 ± 116	6.5 ± 1.5	50
Osborne-Mendel	Control, not depancreatized (57)	264 ± 92	394 ± 143	340 ± 100	446 ± 80	7.2 ± 2.8	75
	Adult pancreatectomy (18)	253 ± 89	377 ± 118	339 ± 111	415 ± 37	5.3 ± 0.9	50
	Immature pancreatectomy (33)	183 ± 83	318 ± 77	285 ± 98	384 ± 60	5.4 ± 1.7	15

*Tests made two weeks after alloxan injection; 100 mg. glucose per 100 gm. body weight in 20 per cent solution given by mouth after twenty-four-hour fast.

†Postprandial blood taken three weeks after alloxan injection.

‡The urine was tested three weeks after alloxan. During the test the animals were placed in metabolism cages for an eighteen-hour period for urine collection; 60 ml. of whole milk was presented to the subject and upon finishing this, only water ad libitum was permitted for the rest of the period.

§Figures in parenthesis show number of animals observed.

‖± indicates standard deviation.

¶Figures that are underscored show a statistically significant difference from control. P values less than 0.01.

sugars were significantly below control levels, urinary glucose excretion was reduced and the incidence of ketonuria greatly decreased.

DISCUSSION

The study demonstrates that an animal strain that normally gives a marked triphasic response to alloxan will no longer do so if deprived of a substantial portion of the pancreas. The finding in the Wistar group that both the initial hyperglycemia and intermediate hypoglycemia are thus curtailed emphasizes the role of the pancreas in producing them. The fact that the Osborne-Mendel strain, from which the triphasic response is normally absent, remains unchanged in this respect after pancreatectomy is not contrary to this view. The conclusion from albino rat experiments supports similar findings in other species. Goldner and Gomori[15] reported that pancreatectomy in dogs effectively eliminates alloxan hypoglycemia.

If, therefore, it is true that insulin release from the pancreas is the basis for alloxan hypoglycemia, the virtual absence of this response in the Osborne-Mendel strain suggests either a deficiency in insulin production by the pancreas or a resistance to insulin action. This is consistent with the known diabetic tendencies of the strain.

That the character of the diabetes produced by alloxan action can also be modified by preliminary partial pancreatectomy has been demonstrated. We are at a loss to explain why this modification was apparent in the Wistar strain only in the animals depancreatized as adults and in the Osborne-Mendel strain in the animals depancreatized in infancy. The effect was to lower the fasting blood sugar in alloxan diabetes and correspondingly to lower the subsequent glucose tolerance curve. In the Wistar strain, which is normally subject to hypoglycemia of fasting in alloxan diabetes, the further lowering of the blood sugar by pancreatectomy made fasting an even more precarious experience. Among the Osborne-Mendel rats, with their strain characteristics of fasting hyperglycemia in alloxan diabetes, the lowering of the blood sugar by pancreatectomy seemed to benefit the diabetic condition. This benefit is further substantiated by a decrease in postprandial blood sugar, glucose concentration in the urine and reduced incidence of ketonuria.

Pancreatectomy has been widely demonstrated to produce a decrease in insulin requirement in diabetes,[16-19] and this benefit has been largely interpreted as being due to the removal of the source of glucagon or the hyperglycemic factor. Mirsky and others[20] have shown in the dog that total pancreatectomy, resulting in loss of the external secretion of the pancreas, so curtails intestinal absorption of carbohydrate as to cause a drop in insulin requirement without reference to any glucagon function. The current experiments are not subject to this criticism, however, because the pancreatectomy was only partial and some secreting pancreas always remained. Where lowering of the fasting blood sugar was obtained, as in the highly significant series of immature-operated Osborne-Mendel rats, the findings are at least not inconsistent with the thought that the hyperglycemic principle of the pancreas may be a factor in determining the character of the diabetic symptoms in an animal.

The study as a whole points to a need for further work on the Osborne-Mendel rat to determine whether

the strain is so overendowed with glucagon or so deficient in insulin supply as studies on this unique hereditary line have thus far suggested.

SUMMARY

Albino rats of the Wistar and the Osborne-Mendel strains were partially depancreatized. Some groups were operated on at thirty to forty days of age while others were operated on at 250 to 350 days of age. Both groups were given alloxan in adulthood to determine the effect of partial pancreatectomy upon the triphasic blood glucose response to alloxan as well as upon the character of the subsequent diabetes. The study reveals:

1. In the Wistar strain, in which a marked triphasic response occurs normally, partial pancreatectomy significantly reduces the initial hyperglycemia and the intermediate hypoglycemia.

2. In the Osborne-Mendel strain, partial pancreatectomy produced no change from the normal response, from which the triphasic feature is characteristically absent.

3. The diabetic state produced by alloxan may be modified by preliminary partial pancreatectomy. Thus in the Wistar strain animals operated on in adulthood and in the Osborne-Mendel strain animals operated on before maturity, the diabetes following alloxan was characterized by a lower fasting blood sugar and subsequent tolerance curve than in uncomplicated alloxan diabetes. Furthermore, the incidence of ketonuria was decreased and the concentration of urine glucose and postprandial blood sugar was diminished in the Osborne-Mendel rats.

SUMMARIO IN INTERLINGUA

Responsa A Alloxano, Modificate Per Pancreatectomia Partial

Rattos albin del racias Wistar e Osborne-Mendel esseva partialmente pancreatectomisate. Certe gruppos esseva operate a etates de inter trenta e quaranta dies, alteres a etates de inter 250 e 360 dies. Omne le gruppos recipeva alloxano post attinger etates adulte con le objectivo de determinar le effecto de pancreatectomia partial super le responsa triphasic de glucosa sanguinee a alloxano e etiam super le character del subsequente diabete. Le studio ha resultate in le sequente constatationes.

1. In le racia Wistar—in que un marcate responsa triphasic occurre normalmente—pancreatectomia partial reduce significativemente le hyperglycemia initial e le hypoglycemia intermediari.

2. In le racia Osborne-Mendel, pancreatectomia partial resulta in nulle alteration del responsa normal, incluse le absentia characteristic del triade de phases.

3. Le stato diabetic que es producite per alloxano pote esser modificate per un antecedente pancreatectomia partial. Assi, in le racia Wistar, animales operate a etates adulte e in le racia Osborne-Mendel, animales operate ante lor maturitate esseva characterisate per un plus basse contento de sucro sanguinee in stato jejun e subsequentemente per un plus basse curva de tolerantia, comparate con animales con non-complicate diabete a alloxano.

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Effect of Experimental Nephrosis on Alloxan Diabetes in Rats

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Widespread acceptance has been given to the idea that a diabetic patient who develops the Kimmelstiel-Wilson syndrome[1] associated with intercapillary glomerulosclerosis shows an amelioration of the diabetes, characterized by a decrease in insulin requirement. Studies to verify this relationship, however, have produced conflicting results. Zubrod et al.[2] reported that patients with this syndrome needed less insulin than they had previously required and had a lower incidence of diabetic acidosis than other diabetics. However, others[3,4] could not substantiate these findings.

The discrepancies in these observations stem primarily from the difficulty of making detailed observations before and after development of renal lesions in a given individual. Such studies, however, are possible in experimental animals. Production of nephrosis in the diabetic rat by the injection of anti-kidney serum results in a patho-physiological state similar to that of the Kimmelstiel-Wilson syndrome. A study has therefore been made of the effects of nephrosis on the manifestations of diabetes in the rat.

METHODS

Male Sprague-Dawley rats rendered diabetic by alloxan were observed during a control period; they were then made nephrotic by the injection of nephrotoxic serum (NTS)[5] and restudied, each animal thus serving as its own control. Measurements were made of serum proteins and cholesterol, blood urea, antecibal and postcibal blood sugar, glucose tolerance, insulin sensitivity and urinary excretion of glucose, nitrogen, sodium and protein.

Four animals received insulin treatment throughout the experiment (Group 1), while five were untreated (Group 2).

Presented at the Seventeenth Annual Meeting of the American Diabetes Association in New York City on June 1, 1957.

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Body weights ranged from 235 to 280 gm. at the onset of the experiment. Alloxan was given by intravenous injection in a dose of 40 mg./kg. as a 3 per cent solution, and metabolic studies were begun five or more weeks later. All rats were force-fed a medium carbohydrate, medium protein diet to ensure a constant food intake. The diet for Group 1 provided a daily ration of 60 calories, 400 mg. of nitrogen, and 3.4 mEq. of sodium, while that for Group 2 provided 58 calories, 460 mg. of nitrogen, and 2.7 mEq. of sodium. Free access to water was permitted in both cases. The dietary differences were a by-product of a change in composition made to facilitate administration by gavage.

In a second experiment, five diabetic male Sprague-Dawley rats weighing 275 to 300 gm. were studied while receiving the same diet as that of Group 2, and again when receiving an isocaloric low protein diet which provided the same amount of carbohydrate but only 75 mg. of nitrogen daily. Daily measurements were made of urinary glucose. Antecibal and postcibal blood sugar concentrations were determined twice during a ten-day control period and again three and ten days after initiating the low protein diet.

The experimental and analytical methods employed were those described previously,[6] except that in the performance of intravenous glucose tolerance tests the amount of glucose injected was 0.75 gm./kg. of body weight, rather than 1.5 gm./kg. as had been used in nondiabetic animals.

RESULTS

Characteristics of Nephrosis. Each animal given anti-kidney serum developed the syndrome of proteinuria, hypoalbuminemia and hypercholesterolemia, as do nondiabetic animals.

In the animals of Group 1 sodium retention occurred during the first five-day period following NTS injection (table 1), and was followed by sodium diuresis approximately equal in degree to the retention. Subsequently, sodium equilibrium or slightly positive balance ob-

TABLE 1

Urinary excretion of nitrogen and sodium by nephrotic-diabetic rats

Group 1—insulin-treated
Group 2—untreated

	Group	Control	Days after Nephrotoxic Serum 0—5	6—10	11—15	16—20	21—25	26—30	31—35
Nitrogen (mg./day)	1	412	377	422	391	372	349	372	335
	2	440	448	421	450	398	387		
Sodium (mEq./day)	1	3.24	1.39	4.65	3.55	3.47	3.06	3.39	3.19
	2	2.77	1.89	2.45	2.80	2.52	2.52		

Nitrogen intake: Group 1—400 mg./day
Group 2—460 mg./day

Sodium intake: Group 1—3.40 mEq./day
Group 2—2.70 mEq./day

Each figure is the mean value derived from four animals in Group 1 and five animals in Group 2.

tained. The animals of Group 2 showed the initial retention but not the subsequent diuresis.

The pattern of nitrogen excretion (table 1) in Group 1 was one of initial decrease, a subsequent short period of increase, and a second prolonged period of decreased excretion. These animals gained weight more rapidly after onset of the proteinuria than they had previously, yet showed no edema. Animals in Group 2 did not show these changes in a consistent manner.

The concentrations of serum cholesterol, serum total proteins and blood urea nitrogen showed the expected changes in direction and degree (table 2). There was no difference between the two groups in this regard.

Effect of Nephrosis on Diabetes. The characteristic changes following injection of NTS are shown for a single animal in figure 1. Glycosuria (table 3) decreased in every animal ($p<.01$). The decrease was not related to

TABLE 2

Changes in blood and serum constituents in nephrotic-diabetic rats

Group 1—insulin treated
Group 2—untreated

Constituent	Group	Control	Days after Nephrotoxic Serum 0—10	11—20	21—30	31—40
Serum proteins (gm./100 ml.)	1	6.6	4.5	5.4		7.2
	2	7.5	5.6		5.9	
Serum cholesterol (mg./100 ml.)	1	98	482	394		218
	2	93	538	472	574	
Blood urea Nitrogen (mg./100 ml.)	1	15	16.5	15.5	10.4	
	2			13		

Figures are mean values derived from four animals in Group 1 and five animals in Group 2.

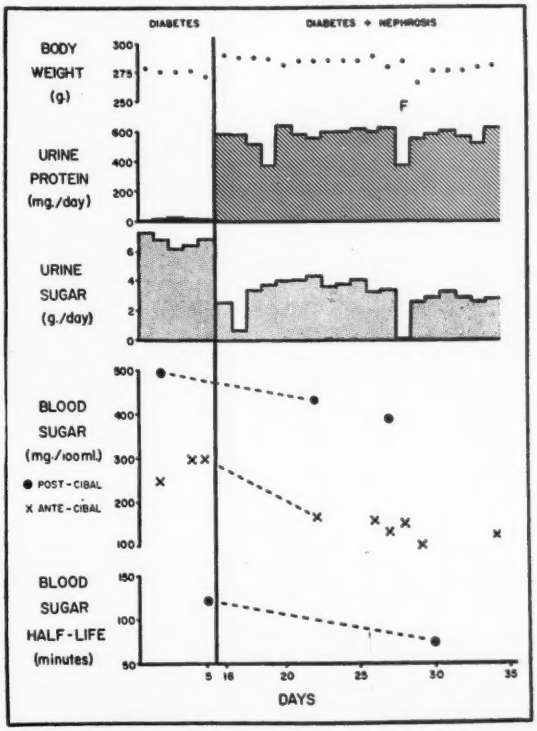

FIG. 1. Effect of nephrosis on glycosuria and glycemia in alloxan diabetic rats. No food was administered on the day designated "F."

the degree of proteinuria within the narrow range observed, or to the degree of glucose excretion in the control period (figure 2 and table 3).

There was a significant decrease in the antecibal blood sugar concentration by 44 ± 17 mg. per cent ($p<.01$). The postcibal blood sugar, measured three hours after

TABLE 3

Effect of nephrosis on carbohydrate metabolism in alloxan diabetes

		Glycosuria* (gm./day)		Antecibal Blood Sugar† (mg./100 ml.)		Postcibal Blood Sugar‡ (mg./100 ml.)		Glucose Half life (minutes)		Fall in Blood Sugar after Insulin (mg./100 ml.)	
Animal	Group	Control	Nephrotic	Control	Nephrotic	Control	Nephrotic	Control	Nephrotic	Control	Nephrotic
11 I-4	1	1.4±.3	.05±.0	187±23	130±7	477 (461-492)	332 (295-371)			110	88
11 I-8		4.0±.4	.85±.0	417±12	347±33	587 (573-600)	501 (443-554)			48	213
11 J-1		3.7±.4	.49±.1	386±36	256±65	663 (631-695)	646 (492-795)	215	77	85	89
11 J-11		1.8±.3	.13±.1	255±20	263±25	463 (450-476)	421 (387-441)	450	13	78	150
11 H-1	2	6.4±.2	4.4±.4	160±14	156±12	404 (394-414)	419 (371-490)	154	54	59	68
11 H-2		6.6±.2	3.4±.2	265±25	147±8	492 (477-507)	417 (387-440)	122	76	141	74
11 M-1		5.4±.2	1.7±.2	130±8	100±14	495 (445-544)	418 (401-435)			41	37
11 M-2		2.9±.1	.29±.1	91±6	108±10	372 (370-374)	229 (188-270)	38	30	39	42
11 M-3		3.5±.1	.15±.1	111±4	102±4	299 (278-320)	194 (185-202)	66	17	48	40
		$p<.01$		$p<.01$		$p<.01$		$p<.01$		$p>.1$	

* Mean ±S.D. (10-20 determinations). † Mean ±S.D. (5-7 determinations). ‡ Mean (2-3 determinations).

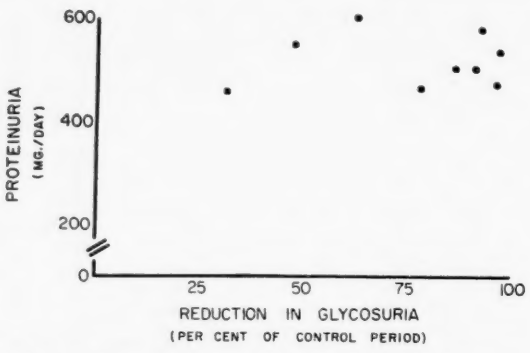

FIG. 2. Relation of proteinuria to the reduction in glycosuria induced by nephrosis in alloxan diabetic rats.

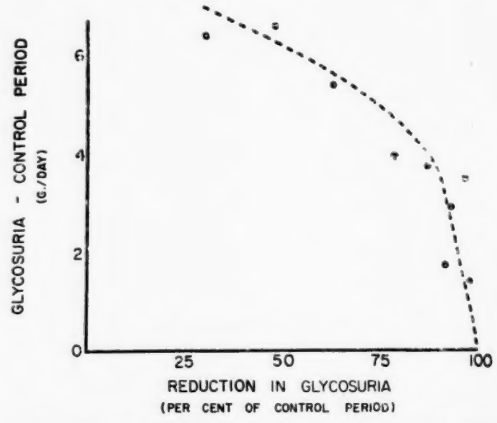

FIG. 3. Relation of glycosuria in alloxan-diabetic rats to reduction in glycosuria produced by the subsequent development of nephrosis.

the regular feeding, was decreased by 76±17 mg. per cent ($p<.01$).

The half life of intravenously administered glucose was decreased in each of the six animals in which it was measured, the degree of improvement being related to the initial half life (figure 4). The blood sugar levels forty hours after the last feeding were essentially the same in the control and nephrotic periods.

Nephrosis produced no change in the response to insulin as determined by the maximum fall in blood sugar (expressed in mg. per 100 ml. or as a percentage of the initial blood sugar) or by the area enclosed by the blood sugar curve below the starting level. None of the differences in response to nephrosis between Groups 1 and

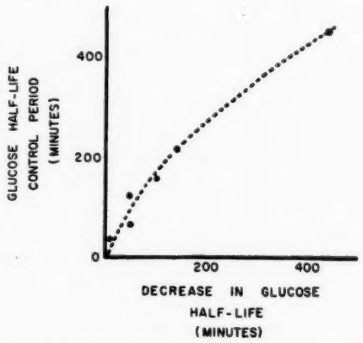

FIG. 4. Relation of the half life of blood glucose in alloxan-diabetic rats to decrease in the half life produced by the subsequent development of nephrosis.

2 was significant at the 5 per cent level.

Effect of Fasting in Nephrotic-Diabetic Rats. Diabetic rats fasted for twenty-four hours showed an immediate fall in sodium and nitrogen excretion and a decrease in blood sugar concentration (table 4). After the development of nephrosis, fasting had similar results and also caused a fall in protein excretion by about 50 per cent. These results are much the same as those previously observed in nondiabetic nephrotic rats.[6]

Effect of Low Protein Diet on Diabetes. Administration of a low protein diet resulted in a fall in glycosuria by $1.73 \pm .02$ gm. daily ($p < .01$). Antecibal blood sugar concentrations fell by 110 ± 39 mg. per 100 ml. ($p < .05$) while postcibal concentrations rose by 25 ± 20 mg. per 100 ml. ($p < .05$).

Pathology. Histological examination of the kidneys of diabetic-nephrotic rats (figures 5, 6) revealed a slight to moderate enlargement of the glomeruli, with many adhesions between the glomerular tuft and Bowman's capsule. Within the tufts there was focal fusion of the capillaries. Staining by the PAS and Lee-Brown technics demonstrated generalized and occasionally nodular thickening of the basement membranes of glomerular tufts and Bowman's capsule. Tubules were dilated and often contained hyaline casts. In some sections the cytoplasm of the tubular epithelium showed many round droplets of PAS positive material, the so-called athrocytes. These changes are essentially the same as those seen in the kidneys of nephrotic, nondiabetic rats.

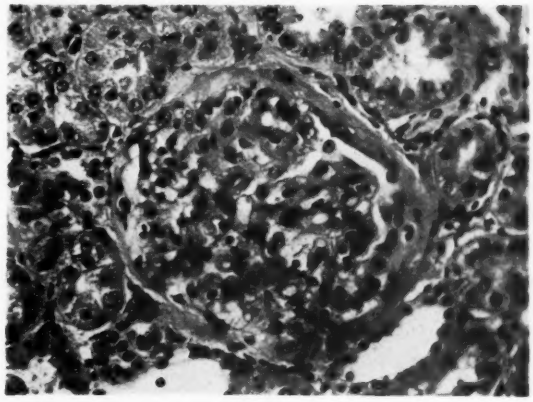

FIG. 5. Kidney of diabetic-nephrotic rat. Glomerulus shows marked thickening of Bowman's capsule and adhesions of capillary tufts to the capsule. Trichrome stain X400.

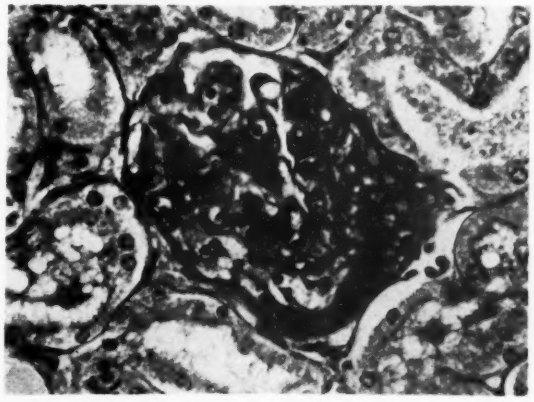

FIG. 6. Kidney of diabetic-nephrotic rat. Glomerulus shows diffuse thickening of basement membrane. PAS stain, X400.

TABLE 4

Effect of fasting in diabetic and diabetic-nephrotic rats

Group 1—Animals treated with insulin.
Group 2—Animals not treated with insulin.

	Group	Diabetes	Diabetes and Nephrosis
Urinary glucose (gm./day)	1	.14	.06
	2	0	0
Urinary sodium (mEq./day)	1	.208	.365
	2	.311	.447
Urinary nitrogen (mg./day)	1	169	147
	2	193	190
Urinary protein % of mean excretion of preceding five days	1	—	48
	2	—	57
Blood sugar (mg./100 ml.)	1	95	119
	2	99	80

None of the differences between the means of control and nephrotic periods was significant at the 5 per cent level.

DISCUSSION

The Kimmelstiel-Wilson syndrome, as originally de-

scribed, consisted of the association of "nephrotic" edema and albuminuria with intercapillary glomerulosclerosis in diabetic patients; hypertension was usually present, with or without azotemia.[1] The glomerular lesion may be diffuse or nodular.[7] In experimental nephrosis of rats the histological changes constitute a "membranous nephritis" comparable to the diffuse type of glomerulosclerosis.

Regardless of the nature or specificity of the renal lesions, it is likely that any effect that the Kimmelstiel-Wilson syndrome may have on the severity of the diabetes is due to the associated metabolic changes of nephrosis rather than to the glomerular lesion directly. Consequently, though the nephrosis in the present work may have differed from the clinical condition both etiologically and pathologically, it nevertheless produced a biochemical status generally indistinguishable from the Kimmelstiel-Wilson syndrome. It may then be anticipated that the changes in diabetes seen in the latter condition would also occur in the present experimental situation.

With the development of nephrosis the diabetes underwent an amelioration, the most striking manifestation of which was the decrease in glycosuria. The degree of improvement was fairly constant, with values of 2.68± .28 gm. per day, and was independent of the degree of glycosuria in the control period, except insofar as the latter constituted the maximum possible decrease (figure 3). It was also independent of the degree of proteinuria. That this change was not a consequence of altered renal excretory function is suggested, though not proved, by the concurrent decrease in both antecibal and postcibal blood sugar concentrations and by the increase in the glucose assimilation rate (reflected in the decrease in half life of blood sugar).

The improvement in carbohydrate tolerance was apparently not mediated by insulin since it occurred without an increase in available insulin or a recognizable increase in insulin sensitivity.

One of the earliest concepts of the metabolic disorders of nephrosis was that of "protein diabetes."[8] This has been re-emphasized in recent work and the proposal made that gluconeogenesis is decreased in nephrotic animals because of "channeling" of metabolites into protein synthesis.[9] There are several reasons which make it appear unlikely that a decrease in gluconeogenesis as a compensation for protein loss was alone responsible for the observed changes in carbohydrate metabolism in the present study:

1. The mean decrease in glycosuria, 2.7 gm. per day, was considerably greater than the mean loss of protein, 0.52 gm. per day. There was thus a net gain of 8 calories daily.

TABLE 5

Effects of nephrosis and low protein diet on alloxan diabetes

	Nephrosis	Low Protein Diet
Protein deficit gm./day (urinary loss or decrease in intake below standard diet)	0.5	2.0
Change in glycosuria gm./day	—2.7±.3	—1.7±.02
Change in blood sugar mg./100 ml.		
AC	—44±17	—110±39
PC	—76±17	+25±20

2. The changes observed when the animals fasted one day showed no difference between the control and nephrosis periods, and specifically did not show an inability of the nephrotic rats to maintain the blood sugar level, a function which depends largely on gluconeogenesis.

3. If the changes were due to the loss of protein in the urine, then they should have been reproduced by a low protein intake. The low protein diet did produce a decrease in glycosuria and in the antecibal glycemia. However, the decrease in protein intake with this diet was 2 gm. per day while the urinary protein loss in nephrosis was only 0.52 gm. per day; yet the decrease in glycosuria was greater with nephrosis than with the low protein diet (2.7±.3 compared to 1.7±.02). Furthermore, nephrosis had led to a decrease in postcibal glycemia and in the postcibal rise in blood sugar; the opposite was true with the low protein diet.

It is possible that hypoalbuminemia and protein deficiency alter the cell membrane so as to decrease permeability to lipids, resulting in hyperlipemia, and increase permeability to glucose, resulting in increased glucose tolerance. This possibility is being examined at the present time.

SUMMARY

1. The effect of experimental nephrosis on carbohydrate metabolism has been studied in the alloxan-diabetic rat.

2. The biochemical and pathological manifestations of nephrosis produced by nephrotoxic serum were essentially the same in diabetic as in nondiabetic rats.

3. Following the injection of nephrotoxic serum there occurred an amelioration of the diabetes, characterized by a decrease in glycosuria, a fall in the antecibal and postcibal blood sugar levels and a decrease in the half life of blood glucose after an intravenous injection of glucose. There was no alteration in the sensitivity to insulin.

4. The ingestion of a low protein diet by diabetic rats led to a decrease in glycosuria and antecibal blood sugar and a rise in postcibal blood sugar.

5. The effects of nephrosis cannot be explained by a decrease in gluconeogenesis, an increase in sensitivity to insulin, or an elevation of the renal threshold for glucose.

SUMMARIO IN INTERLINGUA

Le Effecto De Nephrosis Super Diabete Per Alloxano

1. Le effecto de nephrosis experimental super le metabolismo de hydratos de carbon esseva studiate in rattos con diabete inducite per alloxano.

2. Le manifestationes biochimic e pathologic de nephrosis inducite per sero nephrotoxic esseva essentialmente identic in rattos diabetic e in rattos non-diabetic.

3. Post injectiones de sero nephrotoxic il occurreva un melioration del diabete, characterisate per un reduction del glycosuria, un abassamento del nivellos ante- e post-prandial de sucro sanguinee, e un diminution del medie vita de glucosa sanguinee post injectiones de glucosa per via intravenose. Le sensibilitate a insulina non esseva alterate.

4. Le ingestion de dietas a basse contento de proteina causava in rattos diabetic un reduction del glycosuria e del nivello ante-prandial de sucro sanguinee e un augmento del nivello post-prandial de sucro sanguinee.

5. Le effectos de nephrosis non es explicabile per un reduction del gluconeogenese, per un augmento del sensibilitate a insulina, o per un elevation del limine renal pro glucosa.

ACKNOWLEDGMENT

We are indebted to Dr. K. Wu for preparation and examination of the histological sections.

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DISCUSSION

ARNOLD LAZAROW, M.D., PH.D., (*Minneapolis*): I should like to ask whether the author has any quantitative information on the amount of food consumed by his animals. Is it possible that the decreased glycosuria, the lower blood sugar levels, as well as the decreased turnover rate might all be explained by a decreased appetite and a resulting diminution in food intake?

GARFIELD DUNCAN, M.D., (*Philadelphia*): I would like to ask Dr. Kalant if the decrease in total metabolism associated with removal of the pituitary and adrenal glands might not account in part for the amelioration. Clinically, any circumstance which reduces the total metabolism, with the exception of a decrease in physical exercise, tends to ameliorate diabetes. It would appear possible that in this work reported, two circumstances are at work: primarily, the alteration in the availability of corticoids and, secondarily, a reduction in total metabolic activity.

BENJAMIN JABLONS, M.D., (*New York*): While it is known that nephrotoxic serum exerts its maximum effect on the kidneys, most workers in this field have also observed that there is associated damage to other organs, notably the liver, and I wonder whether damage to the liver might not explain it, unless, of course, damage to the liver has been ruled out in this series of animals.

SOLOMON BERSON, M.D., (*New York City*): If you took out the pituitary in the animals, the diabetes would probably improve. I wonder what the possibility would be that urinary loss of pituitary hormones might produce a partial physiologic hypophysectomy.

JOHN W. RUNYAN, JR., M.D., (*Albany, New York*): I was very interested in this paper since we had suggested several years ago that a possible factor in the decreased insulin requirement occurring in the clinical syndrome of Kimmelstiel-Wilson (i.e., albuminuria, albuminuria and hypertension) was a decreased food consumption with the progression of the syndrome. We further felt that the decreased insulin requirement was not directly related to the specific renal lesion of Kimmelstiel-Wilson. I wonder if Dr. Kalant would comment upon the observation that in this group of patients that we studied that there were eight with the clinical syndrome of Kimmelstiel-Wilson (i.e., edema, albuminuria and hypertension) with six having a significant decrease in insulin requirement, and yet pathologically

showed no Kimmelstiel-Wilson renal lesions?

N. KALANT, M.D., (*Montreal, Canada*): With regard to Dr. Lazarow's question about food consumption, we controlled this by tube-feeding the animals, so that there was a constant food intake throughout the course of the experiment.

With regard to the total metabolism of the animals, we have measured oxygen consumption in nephrotic and control animals, and have observed no difference between them.

Regarding the effect of nephrotoxic serum on other organs, it is true that in the period immediately following the injection of nephrotoxic serum, one can demonstrate, histologically, mild damage to other organs, including the liver and the lungs. However, in animals that survive, these changes disappear, and there remains no evidence, histological or functional, of damage to any organ other than the kidney.

Edema does occur at the time that sodium retention can be seen in the balance data. However, at the time of the sodium diuresis, the edema disappears and does not recur. Consequently, edema played no part in the metabolic changes which we observed several weeks later.

With regard to the question about the fatty liver, I am afraid that we did not examine the livers in the animals on the low protein diet by histological methods. Grossly, they appeared normal. Dr. Berson's question about the loss of protein hormones in the urine, I am afraid that I am completely unable to answer, since we have no way of measuring most of these hormones in the rat urine.

It is certainly true, as Dr. Runyan suggested, that in patients who have the clinical manifestations of the Kimmelstiel-Wilson syndrome, one cannot always find the nodular lesions described by Kimmelstiel and Wilson. However, it has been our impression that one can always demonstrate the diffuse membrane changes in such patients whether or not the nodular lesions are present. The lesions in our animals would correspond to the diffuse lesion and not to the nodular lesion.

Essential Fatty Acids

The term "essential fatty" acids has been used in more than one sense in the scientific literature. In its broadest sense, it has been used to mean all the polyunsaturated fatty acids. Properly, the term essential fatty acids should include those substances which are active both for growth and for maintenance of dermal integrity, limiting the term to linoleic and arachidonic acids and to such other acids as may be derived metabolically from them. In the interest of clarity one should use the specific chemical names of the substances whenever possible.

The common polyunsaturated acids are all straight chain fatty acids having two to six double bonds separated by single—CH_2—groups, and having from sixteen to twenty-two carbon atoms. The most important acids of the group are: linolenic acid, $CH_3(CH_2)_4CH = CH\text{-}CH_2\text{-}CH = CH(CH_2)_7COOH$; linolenic acid, $CH_3CH_2CH = CH\text{-}CH_2CH = CH\text{-}CH_2\text{-}CH = CH\text{-}(CH_2)_7COOH$; and arachidonic acid, $CH_3(CH_2)_4CH = CH\text{-}CH_2\text{-}CH = CH\text{-}CH_2\text{-}CH = CH\text{-}CH_2\text{-}CH = CH(CH_2)_3COOH$.

All the common polyunsaturated acids appear to be related to, or derived from, linolenic, linoleic or oleic acids, and they fall into three groups or families depending upon the structures of their molecules. Those related to linolenic acid have the first double bond between the third and fourth carbon atoms, counting from the terminal methyl group. The substances of this family which have been tested do not maintain dermal integrity, but they stimulate growth. Fatty acids related to linoleic acid (i.e., arachidonic acid) have the first double bond after the sixth carbon atom counting from the hydrocarbon end of the molecule, and these maintain dermal integrity as well as stimulating growth. Acids related to oleic acid have the first double bond after the ninth carbon atom and are presumably synthesized by animals, whereas members of the other two families cannot be synthesized, or cannot be synthesized in sufficient quantities, unless a dietary source of their precursors is furnished. It appears that animals are able to introduce additional double bonds in unsaturated acids between the carboxyl group and the existing double bonds, but are unable to introduce new double bonds between the existing unsaturation and the methyl group at the end of the molecule. For example, it has been shown that arachidonic acid is synthesized from linoleic acid. Members of the individual families thus differ in the lengths of their carbon chains and in the number of their double bonds, but they have similar tail structures. It is also clear that the polyunsaturated acids are not all essential fatty acids in the same sense, and perhaps each individual acid or family of acids may function differently in animal metabolism.

Ralph T. Holman, Ph.D., in *Nutrition Reviews*, Vol. 16, No. 2, pp. 33-34.

EDITORIALS

HYPOGLYCEMIA IN CONGESTIVE HEART FAILURE

Episodes of disordered behavior, coma or convulsions are not infrequent during the course of severe, chronic, congestive heart failure. When observed, they are usually attributed to some process such as anoxemia, a cerebral vascular disturbance, drug intoxication, electrolyte imbalance, or some other alteration directly or indirectly related to the underlying cardiac disorder. The importance of the early recognition of the remediable causes of such occurrences is obvious, and hence the considerable therapeutic significance of the observation that they may occasionally be due to periods of hypoglycemia, readily reversed by the simple act of administering adequate glucose.[1, 2]

Such episodes of hypoglycemia have been observed in a group of patients with chronic congestive heart failure due to a wide variety of causes including rheumatic fever, syphilis, coronary sclerosis and myxoma of the left atrium. The common feature of all of these patients has been congestive failure of very considerable degree and of prolonged duration.

It is not at all difficult to overlook hypoglycemia as the cause of such manifestations as sweating, palpitations, peculiar behavior, lack of responsiveness and convulsions in a patient who is seriously affected by congestive heart failure. The symptoms and signs of hypoglycemia are nonspecific and may be produced by a number of other conditions which are commonly part and parcel of advanced cardiac failure. It is not surprising, therefore, that hypoglycemia has often been overlooked as a cause of these manifestations and frequently recognized ultimately only by virtue of a chance laboratory determination. It is only through constant awareness that hypoglycemia may complicate the course of congestive heart failure and produce these varied alterations that one can apply the dramatic therapeutic as well as diagnostic maneuver of giving glucose to the patient which may be life saving. Before administering glucose it is, of course, helpful to obtain a blood specimen for later determination of the sugar content as a confirmatory test. It is sometimes necessary to give glucose for a prolonged period of time, and afterwards it is essential to make certain that the patient does not relapse into hypoglycemia, unrecognized.

While not demonstrated with finality, it has been postulated that these episodes of hypoglycemia are hepatic in origin, secondary to long-standing chronic passive congestion of the liver, as this has been a common feature of the patients described. Other possible causes of hypoglycemia,[3] including disease of the pancreas, pituitary, adrenals or central nervous system, are thought to have been excluded by post-mortem as well as by clinical observation. It is, of course, possible that other factors may play a role in the production of this hypoglycemia of supposed hepatic origin, namely, anoxemia, failure to eat, and shock secondary to circulatory collapse. It is believed, however, that these could only be contributory factors. Even prolonged starvation does not lead to a significant degree of hypoglycemia. A state of acute or chronic anoxemia is thought to produce hyperglycemia and not hypoglycemia. Shock has never been noted to be accompanied by hypoglycemia.

In any event, it seems clear now that such nonspecific clinical manifestations as sweating, palpitations, disordered behavior, coma and convulsions complicating the course of severe, chronic, congestive heart failure, which frequently are explained away as being circulatory in origin, are occasionally actually due to hypoglycemia. The therapeutic implications of this fact are evident, and one should be alert to it.

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PENTOSE METABOLISM IN MAN

Within the past few years great interest has been demonstrated in the metabolism of five carbon sugars, both in plant and animal tissues. This interest stems from the realization that D-ribose and D-xylulose as phosphorylated esters are important intermediates in the

pentose phosphate pathway of glucose metabolism.[1] In addition, curiosity about pentoses has been stimulated by the observation that D-xylose and L-arabinose infused into eviscerate animals respond to insulin by increasing their volume of distribution in body fluids.[2] The latter observation has lent support to the theory that insulin increases the permeability of cells to sugars of a specified chemical structure.

In normal man small amounts of pentoses are excreted daily in urine.[3,4] Attention has been focused on those states where pentose excretion is excessive, namely congenital pentosuria,[5] pentosuria associated with muscular dystrophy and neurologic diseases,[6] and the alimentary pentosuria seen after ingestion of pentosans.[7] Studies by Touster, Hutcheson and Reynolds[8] have pointed to the defect in congenital pentosuria resulting in the excessive excretion in the urine of L-xylulose. Until recently, little information has been available concerning the metabolism of the pentoses. In 1930 McCance and Madders[9] studied the rates of intestinal absorption of pentoses by human subjects. Experiments have recently been reported describing the dissimilation of infused pentoses in man.[10] D-xylose, D-arabinose, L-arabinose and D-lyxose, when infused intravenously into a normal subject, were observed to disappear slowly from blood. In contrast, D-ribose is cleared from blood at an extremely rapid rate.[11] The clearance of the pentoses (except D-ribose) from blood appears to be independent of the dose. In small doses D-ribose disappears more rapidly than any other sugar. When infused into diabetic subjects deprived of insulin, D-xylose[12] and D-ribose[11] left the blood at normal rates indicating that the mechanism for removal of these sugars is not insulin dependent. Radioactive CO_2 appears in expired air after the intravenous administration of pentose labeled with C^{14} in the first carbon atom except in the case of L-arabinose.[10,13] Approximately 15 per cent of the administered C^{14} is so recovered in six hours. D-ribose, however, differs from the other pentoses by being rapidly metabolized. Fifty per cent of the injected C^{14} was recovered as $C^{14}O_2$ in six hours.[11]

About 50 per cent of infused D-xylose, D-arabinose, L-arabinose, and D-lyxose was excreted in the urine. Much less of infused D-ribose was found in the urine. The results of radioactive tracer studies also indicated the presence of metabolites of the pentoses in urine.[11,13]

Little or no effect of pentose infusion on blood pyruvate and lactate has been observed.[10] Decreases of serum inorganic phosphate values have been noted but the significance of this is open to question. The pentoses, however, do produce an alteration in blood glucose levels. D-xylose and L-arabinose produce slight increases[10] while D-ribose may cause marked decreases of blood glucose values.[14]

The significant lowering of blood glucose after D-ribose infusion has stimulated intensive study. Results of in vitro experiments have suggested that ribose 5-phosphate, a known product of ribose metabolism in mammalian tissue,[15] inhibits phosphoglucomutase, the enzyme which catalyzes the conversion of glucose-1-phosphate to glucose-6-phosphate along the pathway of glycogenolysis.[11] The ribose induced hypoglycemia appears to be due, at least in part, from an inhibition of glucose output from the liver and an interruption of the hepatic homeostatic mechanism for maintenance of blood glucose levels. That ribose causes insulin secretion from the pancreas may also be a factor in explanation of this observation. Hiatt[16] has observed that this response to ribose is not seen in the pancreatectomized dog. The ribose effect on blood glucose seen in man appears to have species specificity since this pentose does not cause hypoglycemia in the rabbit or mouse.[17]

Though a decline in blood glucose occurs after ribose infusion, experiments with isotopic D-ribose indicate that the ribose is rapidly incorporated into the body glucose pool. Glucose isolated from the urine of a diabetic given C^{14} D-ribose has been found to contain the C^{14} with a pattern of labeling which appears to be consistent with operation of the pentose phosphate pathway in man.[11]

Goldstein et al[2] demonstrated in the dog that insulin increased the volume of distribution of the pentoses D-xylose and L-arabinose. In similar studies in man,[18] insulin was found to enhance the disappearance from blood of D-xylose and L-arabinose quite markedly, but little effect was found in the case of D-lyxose, D-arabinose and D-ribose. Calculations indicate that insulin increased the volume of distribution of D-xylose from 20 per cent to 32 per cent of the body weight. These studies show that the most insulin responsive pentoses in man are those which, as Goldstein et al[2] pointed out, have a configuration of carbon atoms 1-3 similar to that of D-glucose.

The insulin responsiveness of D-xylose and L-arabinose in man has been used to compare the actions of insulin and the hypoglycemic agent—tolbutamide. Experiments recently published[19] indicate that although intravenous sodium tolbutamide causes a hypoglycemic response, it produces little or no effect on the blood levels of infused pentoses. The insulin effect on pentoses is presumably due to a peripheral action of insulin. The lack of pentose response to tolbutamide is, therefore, inter-

preted to mean that tolbutamide differs from insulin by neither affecting the transport of sugars across cell membranes, nor stimulating the secretion of insulin.

In human metabolism, these pentoses are negligible from a caloric standpoint. These sugars, however, do play a significant role in intermediary metabolism. Experiments with pentoses in other animal species may be duplicated in man in some but not all cases. Some experiments have indicated effects not observed in other animal species. Still others indicate that pentoses are metabolized in man by as yet unknown pathways. Much biochemical ground has been traversed since the pentoses were regarded as mere structural components of plant and animal tissues. At the present time the true position of pentoses in intermediary metabolism may still be underestimated.

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BLOOD PYRUVATE AND ALPHA-KETOGLUTARATE IN DIABETES

Attempts to classify diabetic patients into groups have utilized various clinical, physiological and chemical criteria. All students have recognized the differences between the older, obese patients with mild diabetes and the young, thin patients with severe disease, easily subject to acidosis. The older French clinicians used the words "Diabète Gras" in contrast to "Diabète Maigre" to differentiate these two types of patients. In more recent years, differences in carbohydrate tolerance and insulin requirements have been common bases for differentiating these two groups of patients. With the introduction of methods for measuring the insulin content of the blood as well as of the pancreas, Lawrence[1] postulated two major groups of diabetics: one obese and middle-aged in whom considerable, though not normal, amounts of insulin could be demonstrated in the blood, and the other thin and young in whom practically no insulin could be demonstrated in the blood. Current studies of the oral hypoglycemic agents also show a different response in these two groups of patients, the obese, mild diabetic proving responsive and the thin, severe diabetic refractive to sulfonylurea compounds. Recently, Smith and Taylor[2] have studied blood concentrations of pyruvate and alpha-ketoglutarate in normal and diabetic subjects and have found differences in the mild, obese group as contrasted with the more severe, thin patients of the Lawrence grouping.

Past studies of the blood concentrations of pyruvate and alpha-keto acids in patients with diabetes have resulted in conflicting reports. Increased blood levels of pyruvic acid and alpha-ketoglutarate have been reported by some workers, whereas others have found normal values for these carbohydrate intermediates in ambulant diabetic patients. A number of workers have reported that little change in blood pyruvate occurs in diabetic patients following the administration of glu-

cose, but in the patients studied by Root, Stotz, and Carpenter,[3] a difference was observed between mild diabetics requiring little or no insulin and patients with more severe diabetes. In milder forms of the disease, a definite rise in blood pyruvate and lactic acid was observed after glucose administration, while this rise was delayed or absent in patients with severe diabetes. The recent studies of Smith and Taylor have confirmed these observations. Their studies were carried out in twelve normal subjects and sixteen diabetic patients. Of the sixteen diabetics six were classified as "obese" and seven as "thin" according to Lawrence's classification. Twenty-four hours after the withdrawal of insulin, and following an overnight fast, the subjects were given a 25 per cent solution of glucose (equivalent to 1.75 gm. of glucose per kg. body weight) by mouth, and blood specimens were collected at intervals of one, two and three hours. A definite and significant increase in blood pyruvate following the ingestion of the glucose was observed in the obese group of patients but did not occur in the group of thin subjects with more severe diabetes. The blood alpha-ketoglutarate increased steadily during the three hours in the thin diabetics; whereas in both the normal and obese diabetics there was a slight increase in alpha-ketoglutarate concentration, followed by a decrease at three hours. These results are of interest, because they document further differences in the carbohydrate metabolism of the obese, mild diabetic and the thin, severe diabetic.

The most probable explanation of the rise in blood pyruvate in the obese patients is that the administered glucose was actively metabolized. In these patients, one might postulate that the obesity was due to their ability to metabolize glucose without added insulin. The absence of an increase in blood pyruvate in the thin patients is evidence of their comparative inability to utilize glucose. This explanation is compatible with the demonstration by Lawrence of the presence of insulin in the blood of the obese diabetics and its absence in the thin diabetics. The authors offer another possible explanation, namely, that a greater glucose diuresis in the thin diabetic group might have caused an increased renal excretion of pyruvate with a subsequent lowering of blood pyruvate levels. However, this does not appear to be a very likely or sufficient rationale. The increase in the level of the blood alpha-ketoglutarate in the thin diabetics, in the absence of any evidence for the metabolism of glucose, as evidenced by pyruvate, is most interesting, and the following two hypotheses may bear on these results.

Alpha-ketoglutarate is not only an intermediate of carbohydrate metabolism in the citric acid cycle, but is also formed in the liver by the de-amination of glutamic acid. Normally, the equilibrium of the alpha-keto-glutaric-glutamic system favors the formation of glutamic acid which may then enter into protein formation. However, in the thin, severe diabetic, fasted and without insulin, protein synthesis is at a minimum; protein catabolism predominates. In this situation, it would be possible to conceive of a reversal of the normal equilibrium, and an accumulation of alpha-ketoglutarate in the blood. Against this hypothesis are the normal (in fact, slightly subnormal) initial levels of alpha-ketoglutarate in these patients. One would have to postulate an increased stimulus to protein catabolism by the administration of glucose.

Secondly, it is of interest to note that both pyruvate and alpha-ketoglutarate, in order to enter the tricarboxylic acid cycle, require as a first step the presence of co-enzyme A to produce acetyl-co-enzyme A or succinyl co-enzyme A respectively. A competition for a common co-enzyme might explain the disparate levels of pyruvate and alpha-ketoglutarate found in these patients.

When hypoglycemia is produced by the administration of insulin, the changes in levels of blood pyruvate and alpha-ketoglutarate may be compared with the changes observed when similar degrees of hypoglycemia are produced by Orinase. In seven normal subjects studied by Hennes, Wajchenberg, Fajans and Conn,[4] the intravenous administration of insulin produced an early rise in the level of blood pyruvate, whereas the intravenous administration of sodium Orinase produced a decline in the concentration of pyruvate. Following the oral administration of 6 gm. of Orinase, the blood levels of these two substances decreased at one hour and increased at two hours. Later changes in blood levels appeared to be associated and to result from hyperadrenalinemia. Their results did not show a constant pattern of change in blood levels of alpha-ketoglutarate in association with hypoglycemia although significant decreases did occur in four experiments in association with Orinase-induced hypoglycemia. The difference in blood pyruvate response suggests that rapid release of endogenous insulin is not the mechanism by which the sulfonylureas produce decline in blood sugar levels in normal subjects.

Other reports at the Conference of the New York Academy of Sciences, Feb. 14, 1957, emphasized differences in levels of these intermediary metabolites in the blood of normal and diabetic humans. Thus Miller, Craig, Mackenzie, Drucker, and Cammarn[5] gave tolbutamide (Orinase) and insulin to each of four normal and

nine diabetic subjects intravenously. On separate occasions, insulin was given in amounts designed to produce a depression of blood sugar similar to that obtained after tolbutamide in the same individual. Under these conditions no definite difference in the pyruvate response followed either agent. The lactate changes were related to hypoglycemia. They concluded that differences in blood levels of pyruvate and lactate reflected differences in the rate of blood sugar depression rather than mechanism of action. However, using a method of hepatic vein catheterization they studied the splanchnic assimilations of fructose, glucose, pyruvate and lactate. Their results suggested that tolbutamide depressed splanchnic glucose production or release during fructose administration. Studies on the site of action of sulfonylureas in man by Renold, Martin, Boshell and Thorn[6] were carried out in an attempt to characterize the hypoglycemia produced by the sulfonylureas as the result of either increased glucose utilization or decreased hepatic glucose release. The decreased conversion rate of fructose to glucose concurrent with sulfonylurea-induced hypoglycemia suggested a decreased rate of hepatic glucose release or synthesis. In addition, these authors, in common with many others, failed to find convincing metabolic evidence of increased glucose utilization as a result of sulfonylurea action, and could not demonstrate increased levels of circulating plasma insulin under these conditions. They regarded these results as providing clear-cut evidence for an effect of the sulfonylureas on hepatic glucose release *in man*, although the possibility of an additional acute effect upon pancreatic insulin secretion was not considered as excluded. Such an effect on insulin secretion *in animals* appears well established.

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Albrecht von Graefe

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The man most deserving of the title, "Founder of Ophthalmology," Albrecht von Graefe, was born in Berlin on May 22, 1828. His father, one of the founders of German surgery, Director of the Surgical Clinic of the University of Berlin and author of many surgical works, was held in high esteem by the royal family. His renown might have been greater, except that he had an untimely death in 1840, and the great Dieffenbach became his successor.

Albrecht received his instruction at home from private tutors, then entered the French Gymnasium, where he attained proficiency in the French language. He was intensely interested in his studies, and at age of fifteen years entered the University of Berlin in the autumn of 1843. He studied logic and philosophy under Carl Ludwig Michelet and demonstrated zeal and intense interest in the natural sciences. The medical faculty at that time consisted of Johannes Muller, Schonlein, Dieffenbach and Juengken, as well as Emil Duboise Reymond, Ludwig Traube, Robert Remak, Rudolph Virchow and Ernst von Brücke. He learned anatomy not only from Muller but also from Schlemm. Among the younger teachers, Graefe was captivated by Virchow.

He had a very happy home and lived in prosperous circumstances. It was his privilege to gain friends quickly and to turn them into enduring friendships. Although his student days were spent in Berlin, he was afforded by his family's wealth and station the opportunity to travel abroad for further studies.

He studied in Prague with von Jaksch, Ditterich and

with Ferdinand von Arlt. Von Arlt was responsible for introducing von Graefe to the study of ocular diseases and surgery, and soon this brilliant young doctor devoted himself to ophthalmology.

The years of 1848 and 1849 were spent in Paris. Much of this time was devoted to study with Claude Bernard, Philippe Ricord and Armand Trousseau. While under the direction of Bernard, he studied intracranial nerves and the extraocular muscles. Clinically, he shared a good deal of time with Julius Sichel from Frankfurt on the Main, founder in 1832 of the first ophthalmological clinic of Paris, and Louis Auguste Desmarres, the founder of the modern French school of ophthalmology.

In 1849 to 1850, von Graefe studied in Vienna. Here he encountered Rokitansky, Bednar, Heschl, Wedl, Brücke, Oppolzer, Bamburger, Hebre and Sigmund. He was especially impressed with the quality of Brücke's lectures on physiology. He also worked on diseases of the eye under Frederick Jager and his son, Eduard. In 1854, Eduard Jager dedicated his book, "Ueber Star und Star-Operation," to his friend, Albrecht von Graefe.

Von Graefe's fame as a teacher and lecturer began in Vienna at that time. A group of young doctors prevailed upon him to lecture to them. He welcomed the opportunity to practice his speaking and teaching.

He left Vienna in July, 1850, and spent two weeks with von Arlt in Prague. From there he went to Berlin and then to London. There have been few finer friendships in the history of medicine than that of von Graefe, Donders and Bowman. It is quite possible that Donders, a physiologist, Bowman, an anatomist, and von Graefe, a clinician, had a significant influence on one another.

Years afterward, in 1886, Donders was selected to present the first Graefe medal, in honor of his lifelong friend, who had since died. In a speech at this presentation, he recalled his first meeting with von Graefe as follows: "I had been enjoying the company of Jaeger for several days, when one morning in Guthrie's Clinic, a young man in full alpine costume burst in. He had only arrived in London a few hours before, and flew into von Jaeger's arms. With the words, 'Here, you two belong together,' the latter literally threw him into my arms. He was not wrong. From early morning after we gathered up a hasty breakfast in Oxford Street and followed the footsteps of the workmen on our way to Moorefield's Hospital until late in the evening when we departed from the hospitable home of our friend, William Bowman, we remained together, inseparable in our search for the common goal. Von Graefe led me in practical matters in which I had, as yet, scarcely delved, and I, in turn, could help him with many things from the physiologic aspect. There lay for both of us in this mutual complimentary relationship a great stimulus. Those days in which von Graefe gradually displayed the fairness of his nature belong to the loveliest recollections of my life. When I left him after several weeks he had become like a young brother whom I admired and loved." (Donders)

When von Graefe set up his practice in Berlin, there were no free clinics exclusively for eye patients. He modeled his first clinic after that which he had seen in France. This was done in the second story of a house in Behrenstrasse. Shortly thereafter, two simple rooms were rented from a tailor in Johannestrasse, furnished with beds and readied to receive the operated cases. Such was the start of the famous Graefe Clinic, which, after one decade, was to receive patients from all sections of the world. Actually, at this time, there was an advertisement in the daily Berlin newspapers saying, "Dr. Albrecht von Graefe in Behrenstrasse. Eye diseases treated free for the poor." (Adler)

His first cataract extraction was performed on an old inmate of a poorhouse; at the same time, an iridectomy was done on an organ-grinder, who had an old, adherent leucoma, the result of ophthalmia neonatorum. Two nights after the operation, the patient with the iridectomy lost his mental equilibrium as a result of the bandages and attacked the patient with the cataract to such an extent that the cataract patient died. Subsequently, the iridectomized individual recovered and was able to walk unguided for the first time in his life.

By the time von Graefe was twenty-five years old, he had over 1,900 patients recorded in his clinic, and a few years later he had over 10,000 on record. According to Michaelis, von Graefe devoted his mornings to private consultation, operations in the clinic, and then, after lunch, to physiologic studies, and evenings, after hospital visits, to scientific investigations. Later, he adopted a different schedule to which he thereafter adhered. During the mornings he devoted himself to literary pursuits, then lectures, hospital visits and occasional consultations in the city; after lunch, work in the outpatient department and operations and, in the evening, consultations with private patients followed by a visit to the hospital and, finally, a short period of recreation with friends. It is obvious that such a routine must have weakened him and paved the way for his later years of illness. (Michaelis)

Von Graefe transferred the hospital and clinic to 46 Karlstrasse, where both remained until his death. Now a simple tablet announces to the observant visitor. "Hier Wirkte 1852 bis 1870 Dr. Albrecht von Graefe."

In the autumn of 1852, Graefe qualified as Privatdocent der Chirurgie und Augenheilkunde in the medical faculty of the University of Berlin with a treatise entitled "On the Action of the Ocular Muscles." His tie with the University was a very loose one. By virtue of his position as Privatdocent, he was not permitted to post a notice of his course unless he was in charge of the clinic. He therefore devoted his time to teaching the doctors who came to him from all parts of the world. Very few medical students came under his direction or attended his lectures or clinics at that time. After the first few years, by which time his fame as a teacher had spread, he devoted himself chiefly to the clinic and had assistants who gave most of the basic courses.

In 1854, Graefe established the *Archiv für Ophthalmologie*. This journal filled the need of ophthalmology for its own journal, for there was considerable basic scientific investigation now being done in this specialty. The major advance, however, which showed the necessity for such a publication, was the discovery of the ophthalmoscope by Helmholtz. Epstein has recorded the letter which Albrecht von Graefe wrote to Helmholtz about 1852, shortly after his return from his three-year journey to the medical centers of Europe. He was twenty-four years old, and at that ripe young age he recognized the great discovery made by Helmholtz. (Epstein)

Esteemed Professor:

You will pardon the liberty of addressing you, an utter stranger, and requesting a favor concerning a subject which interests me greatly. Last summer, I learned through Professor Brücke in Vienna that you have succeeded in constructing an instrument for examining the retina in the living eye. I even had the pleasure of hearing some of the details by means of which you accomplished this. Professor Brücke was more willing to indicate these to me since we frequently talked over the possibility of such an instrument, and he had previously shown me a scheme of his which had miscarried because of the lack of suitable illumination. Brücke expected to obtain the catoptric and dioptric effects from his instrument by means of a concave glass placed at an oblique angle over the observed eye.

The news of your successful accomplishment was therefore the more welcome to us, and I awaited the publication with impatience until a few days ago, when I was fortunate to find it waiting for me on my table on my return to Berlin after a long journey. To the study of this article I am not only indebted for an exact understanding of the instrument but also for the explanation of other questions in optics which were quite closed to me, and am therefore going to ask you if you will kindly request your optician to send one or two of your finished ophthalmoscopes to my address in Berlin.

The first number of the journal contains 480 pages, most of which are written by the young editor. Soon he was assisted in the editorship by Arlt, of Vienna, and Donders, of Utrecht.

In 1857, he was appointed Assistant Professor at the University of Berlin. This did not change his activities. In this same year he reported on the possibility of curing glaucoma by iridectomy. His presentation of this information at the International Congress of Ophthalmology at Brussels, in 1857, evoked a storm of applause from the leading scientists of the world. Also in the fall of 1857, he and a few of his friends gathered at Heidelberg to talk over the progress of ophthalmology. Thus was established the oldest local ophthalmological society in existence, the Deutches Ophthalmologisches Gesellschaft. (Axenfeld)

When von Graefe was thirty-three years old, he was engaged to marry Anna Gräfin Knuth, a charming girl not quite nineteen years old. However, while he was on vacation in the fall of 1861 in Baden Baden, he developed tuberculous pleurisy. Under the excellent nursing care of his two sisters, his bride-to-be and his boyhood friend, Dr. Arndt, and the medical ministrations of Dr. Müller, Professor Friedrich from Heidelberg and Professor Traube of Berlin, the disease was arrested. He continued his convalescence in Nice and finally was married on June 7, 1862. He had several very happy years. His wife often wrote down his dictation until he obtained his own secretary. In the short period of their married life, five children were born. The second child died at the age of six months, and the last child, a son born on July 2, 1869, lived for only a few days. Von Graefe was a modest man who enjoyed good food and drink, but in moderation. He loved company at dinner. He occasionally attended the opera and theater but was rarely seen in public, spending most of his time with his patients and his clinic and his pupils. For him, his greatest pleasure was to be found in his work.

Hirschburg met von Graefe in 1866 and found him to cast a spell over everyone with whom he came in contact. He was impressed with his extraordinary beauty, and remarked on his tall, slender figure, noble brow and classic countenance, ringed by a dark beard and long, curly hair. The sound of his voice and the penetrating keenness of his gaze established great confidence in his patients. (Hirschburg)

In 1866, he was appointed full Professor on the medical faculty of the University of Berlin. His lectures were

not well attended by medical students, perhaps because examinations in ophthalmology were not obligatory. Some have expressed the feeling that his lectures were too intricate for medical students. At the Seventy-First Anniversary of the founding of the Friedrich Wilhelm Institute, Aug. 21, 1865, Graefe devoted his public address to the subject of the importance of ophthalmology in general medicine. He was not very happy with the medical faculty, nor did he receive much support from the faculty or from the government. He did not receive a Directorship of the Konigliche Klinik by his appointment as Professor, and he had considerable difficulty obtaining adequate hospital facilities for the patients who were to be used as his teaching material. In a letter to Jacobson in 1868, he displays his feelings. "My situation is this; I am of course a Professor. I receive as such 500 thaler salary. I do not give examinations, since Papa Juengken still takes care of that in an uncurtailed manner and, naturally also collects remuneration. For this 500 thaler—up to now there has been no talk of the Konigliche Clinic—I have to obtain teaching material for sixty or seventy students, of whom the majority wish to become specialists. Actually I dare not reduce the hospital division of sixty beds in my clinic in order to suffice for their requirements. It costs me in order to have the good fortune to be a teacher of ophthalmology . . . another 5,000 thaler a year." (Jacobson, Perera)

In 1866, Graefe finally became the Head of the Charity Ophthalmologic Clinic, and by 1868, ophthalmology became an essential part of the medical requirements. In the same year, unfortunately, his pulmonary disease became more active. So did his own activities. As disease weakened him, he doubled his efforts to carry out his work. He did not seem concerned with his own illness, but only that of his wife. By 1869, his cough and hemoptysis almost incapacitated him. He was unable to attend the meeting of the Gesellschaft at Heidelberg. Donders called upon him after this meeting to tell him about it, and to sympathize with him. At this time, von Graefe quoted the words of Goethe, "One cannot learn too soon how really unessential he is in the world." On July 20, 1870, he died at the age of forty-two.

It is difficult to select one thing for which von Graefe is famous. He gave great impetus to the development of ophthalmology. He started the *Archiv für Ophthalmologie.* He devised the operation of iridectomy in the treatment of glaucoma, which is still the most widely employed operation for angle-closure glaucoma. The Graefe knife is extensively used for cataract extraction. He was one of the first to describe the cupping of the optic nerve in advanced glaucoma and to attribute the changes in glaucoma to an increase in intraocular pressure. He described the edema of the nervehead associated with intracranial disease and the signs of blockage of the central retinal artery.

A complete list of his contributions can be found in Perera's review of life and works, in which one will find that he wrote in 1858 on the visual disturbances in diabetes mellitus, describing the diabetic cataract in young and old persons, chronic choroiditis and cerebral amaurosis as complications. In many diabetic patients, he had observed weakness of accommodation. He is probably most widely remembered as the first to use in clinical practice the ophthalmoscope invented by Helmholtz. In Graefe's words, "Helmholtz gave us a new world." He was one of the first to begin systematic plotting of the fields of view in cases of defective vision.

Von Graefe became the first German professor of ophthalmology. In his short, exhausting, but productive life, he did not demonstrate the inventive genius of Helmholtz or the ability to work with minute instrumental detail, as had Gullstrand, but because he had the tremendous ability to apply new methods of examination to their utmost clinical use, to take his clinical observation and deduce with great detail reasons for their existence, he established the scientific foundation of modern clinical ophthalmology. He was one of the first to describe transillumination for the detection of tumors, to use an instrument for the measuring of the tension of the eyeball, to make clinical records of the pathological visual field. There is hardly an area in clinical ophthalmology to which he has not contributed.

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BOOK REVIEWS

LIVER: STRUCTURE AND FUNCTION. *By Hans Popper, M.D., Ph.D., and Fenton Schaffner, M.S., M.D. $20.00, pp. 777, The Blakiston Division of the McGraw-Hill Book Company, Inc., New York, 1957.*

Dr. Popper's and Dr. Schaffner's first edition has been eagerly anticipated since its announcement. It not only completely fulfills all expectations but also exceeds them. It will prove an invaluable aid to all students of hepatology.

The work is organized under seven broad headings: (1) normal structure and function, (2) pathologic phenomena of the hepato-biliary system, (3) clinical studies of hepatic function and structure, (4) diffuse diseases of the liver, (5) focal diseases of the liver, (6) tumors of the liver and biliary tree, and (7) internal and external environment of the liver. An appendix summarizes principles of diagnosis of liver disease using functional and structural observations. An extensive bibliography of 3,735 untitled references is arranged alphabetically thus obviating the need for an index of authors. The subject-index is comprehensive and cross-referenced. Two hundred and four diagrams or photomicrographs and sixty-two tables adequately supplement the text. The photomicrographs are of the excellent quality that has characterized Dr. Popper's publications in the past, although some may have suffered in the process of reproduction. Inclusion of many of Hans Elias' three-dimensional reconstructions add interest and clarity.

Coming from an eminent pathologist and expert internist, one might have expected greater emphasis on disease and less on anatomy, physiology and biochemistry. The latter sections are welcome and should be valuable to nonspecialists in these areas for rapid reviews of modern concepts relating to the liver. But in view of Dr. Popper's broad experience and continental background, this reviewer was disappointed to find that the pathology of the liver is not presented in exhaustive and comprehensive detail as in Henke and Lubarsch, for example. An up-to-date English counterpart of the latter work is as badly needed for liver as for other organs. The space devoted to normal aspects of the liver and more purely clinical considerations has not allowed Dr. Popper to give us this type of pathologic *arbeit*, of which we know he is fully capable.

Within the space available, however, the pathologic aspects of liver disease are admirably presented. Clinical aspects are clearly described, including summaries of technics in fine print. The brief chapter (six pages) on liver biopsy contains the distilled essence of both authors' experiences. Much of the confusion in current concepts of cirrhosis, postnecrotic scarring and chronic hepatitis is clarified in the section on diffuse liver disease. The section on tumors, although limited in scope, is accurate and clear. In our opinion, the weakest portion of the book is the last, in which an attempt has been made to relate the liver in various states to other organs (hematopoietic system, etc.) and even to "stress"!

The book is remarkably free of typographical errors for a first edition. The two-column format somewhat alleviates the size and ponderosity of the volume and the print is clear and legible. The incorporation of an addendum at the end, in which are included recent advances published while the rest of the book was in print, has successfully kept it up-to-the-minute as of its publication date. This novel technic should be more widely adopted by authors and publishers of books in rapidly advancing areas of medical investigation.

Popper and Schaffner deserves a place on bookshelves of clinician, pathologist and student. We expect this work will soon takes its rightful position as leader in its field and pass through many editions.

COUNSELING IN MEDICAL GENETICS. *By Sheldon C. Reed. $4.00, pp. 268, W. B. Saunders & Co., Philadelphia, 1955.*

This book, though small, should prove invaluable to the physician who is aware of genetic problems as they affect clinical medicine and will, I believe, stimulate such awareness in others. It is well written and thoroughly indexed. Chapter Three, "A Philosophy for Counseling," is an excellent expression of the ideal attitude a physician should take. Because of the nature of the subject and the brevity of the book, many physicians truly interested in the proper counseling of their patients will have to refer such patients to a counseling center in many instances, but the purpose of the book is not to cover the entire field but rather to stimulate an interest and to show the possibilities in genetic counseling.

Not all geneticists will agree with some of the methods of inheritance as postulated by the author and not all physicians interested in the subject will agree with his selection of diseases. Many of the more common clinical problems which have a genetic background are omitted but this does not detract from the book as a whole, since to cover everything would require several volumes. The main function of the book as mentioned above has been more than adequately fulfilled and this volume should find a useful place in the library of every family physician.

MEDICAL PROGRESS, A REVIEW OF MEDICAL ADVANCES DURING 1956. *By Morris Fishbein, M.D., and twenty-nine contributors. $5.00, pp. 350, The Blakiston Division of the McGraw-Hill Book Company, Inc., New York, 1957.*

The nineteen chapters of this book contain progress in medicine, surgery, obstetrics and some subspecialties. There are twenty-nine contributors chosen "because of their ability to present, briefly and succinctly, new concepts, conclusions, methods and their applications." These goals were attained.

In general one is impressed firstly by the development of new drugs and secondly by advances in methodology.

The tranquilizers lead the field with some twenty-eight preparations. The three latest additions, mepazine, promazine, and atarax, are described in full—their uses, dosages and hazards. These drugs have found wide use in mental hospitals and though their action, as stated in the book, is not clearly defined, they are nevertheless "effective in making disturbed mental-hospital patients more accessible to treatment. . . ." There is also the salutary warning that the last word has not been written about them. Descriptions also are given of new antibiotics, antihypertensive drugs, the sulfonamides for oral use in diabetes mellitus, and the use of relaxin in obstetrics.

Methodology has made advances in diagnosis and treatment. Much that has been learned in cardiovascular surgery has been reported—the use of hypothermia, the surgical approach in the treatment of Parkinson's disease, and hypophysectomy in the treatment of cancer and diabetes mellitus. The use of various radioactive isotopes is fully discussed and mention too is made of cineradiography as an aid in the study of gastro-enterologic problems.

In a work compiled by so many, overlapping may result if the editing is liberal. The chapters on diabetes and endocrinology contain some similar material, an unnecessary duplication. The chapter on endocrinology is truly saturated with so many facts that unless one is devoted to this particular field he may find it difficult to follow.

The chapter on nutrition presents an excellent discussion on the relation of diet to atherosclerosis with the cogent conclusion that "until the status of essential fatty acids in relation to cholesterol metabolism is clarified, judgment can not be made concerning the possible desirability of advising patients to make major changes in their eating habits purely as a preventive measure."

Each chapter is informative, clear, and is followed by an extensive bibliography enabling the reader to have ready access to references should he wish to explore further some points of particular interest to him.

Over-all, this work summarizes well the medical developments of 1956 and will be quite helpful to all who find it practically impossible to keep up with the enormous medical literature which appears annually.

OBESITY, ITS CAUSE, CLASSIFICATION AND CARE. *By E. Philip Gelvin, M.D., and Thomas H. McGavack, M.D. $3.50, pp. 140, Hoeber-Harper, New York, 1957.*

The first twelve pages of the book discuss the definition and clinical features of obesity. The authors then discuss the anatomy and physiology of adipose tissue per se and the intermediary metabolism of carbohydrates and fats including the Krebs' cycle. There is a chapter on the classification of obesity which follows the traditional concepts. The management of obesity is presented as a condensed version of several of the current concepts. In the reviewer's opinion, emphasis on overeating as an outlet for psychic stress is too great.

The basic thesis of the book is the conventional one that obesity is due to an intake of calories in excess of energy output. However, the discussion of energy output and exercise occupies only one and one-half pages of the book. Data are now available indicating that 100 calories a day between activity and inactivity are indeed very common. The authors have focused so much attention on food intake that they have understated the importance of the energy output aspect of this story. On page fifty-seven they state: "In our study of the subjective impressions of overweight individuals as the cause of their obesity only two of the 108 patients questioned attributed their obesity to inactivity." Yet throughout the book they repeatedly point out that the patient's comments on food intake are unreliable.

The dietary management of the patient occupies approximately seventeen pages in all. The book simplifies the dietary aspect and gives only two diets with a limited number of substitutes. These diets are a 1,000-calorie diet and a 1,200-calorie diet. In the reviewer's opinion, the difference between a 1,000-calorie diet and a 1,200-calorie diet as consumed can be negligible. A difference in the meat course between sliced chicken and hamburger can be 150 calories; between a serving of codfish and lamb chops can be 160 calories. The diets as presented contain fairly high fat foods. The 1,000-calorie diet, for instance, allows two pats of butter and recommends such items as liverwurst. In their meat substitutes they pick some high fat meats such as veal chops, veal cutlets, lamb chops, and meat patties. There is no mention of cooking procedures and only

minor cautions as to the use of fats or oils in food preparation. Pages eighty-seven and eighty-nine contain an abbreviated list of low-calorie vegetables classified A and B. The instructions under A are confusing. They state "—use freely if served raw. Use one cup at a meal if cooked; if taken in excess of this amount calculate as list B vegetable." List B states "You may use these vegetables raw or cooked one-half cup."

One of the major parts of the book is directed towards a discussion of the anorexigenic agents, particularly the amphetamine preparations. Their views of the subject are indeed optimistic. They report that only 17 per cent of their patients develop subjective symptoms: basically excitatory effects as insomnia, nervousness, palpitation, and mild gastrointestinal disturbances. They do refer to the "conference on therapy devoted to the treatment of obesity" which appeared in the *American Journal of Medicine* in 1952 as not having reported the same results with the anorexigenic drugs. Their discussion on endocrine preparations is limited.

A confusing aspect of the book is the short discussion of the termination of the treatment. The patient is instructed to weigh himself weekly, and if he continues to lose weight to increase his intake of food. If his weight exceeds the maximum allowed him, he is to decrease his intake towards the original diet. By a process of trial and error the patient is said to learn what he can eat and yet maintain a desirable weight. This advice presupposes a detailed knowledge on the part of the patient of what constitutes his dietary problems. It must not be forgotten that these people were obese to start with because they did not understand the basic principles of their dietary requirements. Few patients can learn to manage their own treatment so quickly without more detailed suggestions.

The authors state that they use and advocate a general diet made up of ordinary everyday foods with an average distribution of proteins, carbohydrates and fats. In their opinion it encourages cooperation by the patient since the adjustment he has made is only quantitative and not qualitative.

Patients who are sincere about wanting to lose weight make this adjustment readily in about three to five weeks. Therefore, they write, "the problem of dietary adherence is not too great."

One gathers from reading this book that the authors depend upon the anorexigenic drugs to a great extent. The diet instructions and re-education of the patient's eating habits are not stresssed sufficiently in the opinion of the reviewer.

THE TREATMENT OF RENAL FAILURE. *By John P. Merrill, M.D. $6.75, pp. 229, Grune and Stratton, Inc., New York, 1957.*

Since the treatment of renal failure depends on an understanding of the functional pathology of the kidney and the consequent biochemical changes in the body fluids, this monograph properly begins with normal renal physiology and composition of body fluids. There follows the discussion of renal insufficiency and the various signs and symptoms of renal failure. The chapters on renal water and electrolyte excretion and the clinical effects of sodium and potassium losses are excellent, though rather concentrated.

The first chapter on treatment (V) begins with a classification of the numerous causes of acute renal failure and a separate listing of the reversible group, namely obstructive uropathy, acute pyelonephritis, circulatory insufficiency (cardiovascular failure or body fluid loss), chemical nephrotoxins and intravascular hemolysis. The details of management in the reversible group follow accepted principles and are very well described, both from a practical standpoint and their scientific basis. This chapter is the quintessence of the author's experience and of the book. Mastery of its contents by physicians should help save many lives.

The discussion of the treatment of chronic renal failure is adequate and includes an excellent analysis of the problem of protein metabolism in renal disease. In addition to detailed "do's," the author emphasizes some "don'ts" and gives due credit to the "wisdom of the body" and its compensatory mechanisms.

The last four chapters are concerned with extrarenal routes of treatment of renal failure, by means of intestinal or peritoneal lavage, replacement blood transfusions, the artificial kidney and the transplanted human kidney. The approach is conservative but with an urgent plea for early consultation with a "dialyzing center" in regard to the use of the artificial kidney. One cannot disagree with the author that a definite time limit should be set for conservative treatment in acute renal crises. The indications and contra-indications to dialysis in chronic renal failure are clearly defined, and the expectations from the procedure are kept within reasonable limits.

The bibliography includes 302 references, of which 86 per cent cover the years 1945-55. One misses many of the historical names and classic papers in the field of Bright's disease. On the other hand, there is no reference to electron microscopy of the glomerulus.

The expressed purpose of this monograph—to serve as a guide to treatment—is fully accomplished.

ABSTRACTS

Akishina, N. I.; Balen, S. A.; Genes, S. G.: Kaplan, P. M.; and Sukhovoi, F. I. (Ukrainian Inst. of Experimental Endocrinology, Kharkov, USSR): CHRONAXIE OF THE NEURO-MUSCULAR APPARATUS IN PATIENTS WITH DIABETES MELLITUS. Vrac. Delo 9:843-44, 1955.

Newly admitted patients who had not had insulin showed shortening of chronaxie more frequently than patients who had received insulin. These differences were more prominent in the chronaxie of muscles than of nerves. During their stay in the clinic (three to four weeks), when the patients received insulin and a rational diet, the chronaxie failed to return to normal (except in a few cases) in spite of the general improvement in the patients' condition. Often the chronaxie became normal two to four months after discharge from the clinic. (Russian)

Bell, E. T. (Dept. of Path., University of Minnesota, Minneapolis, Minn.): CARCINOMA OF THE PANCREAS: I. A CLINICAL AND PATHOLOGIC STUDY OF 609 NECROPSIED CASES. II. THE RELATION OF CARCINOMA OF THE PANCREAS TO DIABETES MELLITUS. Am. J. Path. *33*:499-523, May-June 1957.

The author concluded that there is a high incidence of glycosuria and hyperglycemia in association with carcinoma of the pancreas. No sharp distinction can be made in carcinoma of the pancreas between simple glycosuria and diabetes. If we exclude those cases of diabetes in which the symptoms of cancer antedated or were concurrent with the recognition of diabetes, then the incidence of diabetes in subjects with carcinoma of the pancreas is not significantly greater than its incidence in the general necropsy population of corresponding age. Diabetic patients with carcinoma of the pancreas differ from other patients with diabetes in the shorter duration of the diabetes as well as in the decreased frequency of hyaline islets in the pancreas and vascular renal changes. Carcinoma of the pancreas produces glycosuria probably more by interference with the escape of insulin from the pancreas than by actual destruction of islets. The total incidence of cancer in diabetic patients is less than one half its incidence in nondiabetic patients. According to the data presently available, which are admittedly inadequate, carcinoma of the pancreas comprises three times the proportion of total cancer in diabetic patients that it does in nondiabetic patients.

Bergstrand, A.; and Bucht, H. (Karolinska Inst., Sabbatsbergs Sjukkus, and 3rd Med. Clin. of St. Eriks Sjukhus, Stockholm, Sweden): ELECTRON MICROSCOPIC INVESTIGATIONS ON THE GLOMERULAR LESIONS IN DIABETES MELLITUS (DIABETIC GLOMERULOSCLEROSIS). Lab. Invest. *6*:293-300, July-August 1957.

The electron-microscopic pictures show that the specific glomerular lesions in diabetic glomerulosclerosis consist of a thickening and folding of the capillary basement membrane accompanied by a precipitation of a "hyaline" material in the cytoplasm of the endothelial cells and a proliferation of these cells. The name "intercapillary glomerulosclerosis" is therefore inadequate and should be discarded. Changes are also observed in the basement membrane of Bowman's capsule. It is probable that all these changes are of the same nature and are part of a metabolic change in the mucoproteins. This concept lends support to the assumption that the capillary basement membrane is a part of the endothelial cell.

Burckhardt, W.; Burckhardt, K.: and Schwarz-Speck, M. (Dermatological Clinic, Univ. of Zürich, and Municipal Policlinic for Skin Diseases, Zürich, Switzerland): PHOTOALLERGIC ECZEMAS DUE TO NADISAN. Schweiz. Med. Wchnschr. *87*:954-56, July 13, 1957.

Two diabetic patients treated by carbutamide (Nadisan) developed eczema on their face, neck, hands and forearms. Carbutamide applied to the skin did not cause any reaction unless the skin was exposed to sunlight or ultraviolet rays. Tolbutamide, used to replace carbutamide, was well tolerated. (German)

Burton, Stanley D.; Robbins, Edward; and Byers, Sanford O. (Harold Brunn Inst., Mount Zion Hosp., San Francisco, Calif.): EFFECT OF HYPERTHYROIDISM ON GLYCOGEN CONTENT OF THE ISOLATED RAT LIVER. Am. J. Physiol. *188*:509-13, March 1957.

A method is described for determining net changes in glycogen content of the isolated rat liver after six hours of perfusion using the glycogen content of the caudate lobe of the liver as a control value. Experiments were performed in which livers obtained from normal and hyperthyroid rats were perfused at low and high perfusate glucose levels and the glycogen content of the livers determined before and after perfusion. It was found that the isolated liver from the untreated rat under artificial perfusion neither increased nor decreased appreciably in glycogen concentration during a period of six hours at either low or high glucose perfusate concentrations. In contrast, the isolated liver from the hyperthyroid rat, which is uniformly low in glycogen concentration, increased in glycogen concentration markedly by the end of perfusion at high perfusate glucose concentration (above 600 mg. per cent). Conclusion: The data confirm the ability of thyroxine to deplete the liver of its glycogen content and establish that thyroxine influences the metabolism of the hyperthyroid liver and its enzyme systems to promote glycogen storage even in the presence of increased glucose metabolism.

Butterfield, W. J. H.; Fry, I. Kelsey; Hardwick, C.; and Holling, H. E. (Medical Research Council and Guy's Hosp., London, England): TOLBUTAMIDE IN TREATMENT OF DIABETES MELLITUS. Brit. M. J. *2*:325-27, Aug. 10, 1957.

The authors comment on the efficacy of tolbutamide therapy in diabetes mellitus and suggest criteria for selecting patients as well as a method of testing the patients' response to the drug.

Cohen, Aharon M. (Dept. of Med., Harvard Med. Sch.; Med. Res. Dept., Yamins Res. Labs. and Med. Serv., Beth Israel Hosp., Boston, Mass.): INTERRELATION OF INSULIN ACTIVITY AND THYROID FUNCTION. Am. J. Physiol. *188*:287-94, February 1957.

The effect of variation in thyroid status on insulin metabolism and glycogen synthesis has been studied in rats. In vitro incubation of rat diaphragm with 0.1 mg. triiodothyronine or

0.1 mg. thyroxine for thirty and forty-five minutes had no effect on I^{131} insulin uptake of the diaphragm. Daily intraperitoneal injections of 50 γ triiodothyronine increased oxygen consumption and had an increasing effect on in vitro insulin diaphragm uptake, beginning after two days, reaching a maximum of 32 per cent over controls on the fifth day. With continued administration of triiodothyronine, diaphragm insulin uptake declined to control levels on the twelfth day of triiodothyronine administration. During the first two minutes after intravenous administration of I^{131} insulin in triiodothyronine-treated animals (50 γ daily, i.p. for five days) muscle showed an increased uptake of insulin. There was a subsequent progressive fall in tissue uptake to approximately levels found in control animals. Blood radioactivity disappeared more rapidly after injection in the thyrotoxic animal than in the control of hypothyroid rats. Glycogen deposition (insulin-glycogen effect) in the thyrotoxic animals was greater than in controls. However, while tissues from control animals continued to deposit glycogen at the same rate, the diaphragm from thyrotoxic rats showed, after thirty minutes of incubation, a marked fall in glycogen synthesis. Glycogen synthesis in diaphragms from triiodothyronine-treated animals incubated in glucose alone without insulin equilibration was the same as in control diaphragms. These studies indicate that thyroid has a direct effect on insulin metabolism; there is a lag before the action of thyroid becomes manifest, and the initial effects subside as other effects of the thyrotoxic state influence insulin and carbohydrate metabolism.

Conard, V.; Christophe, J.; Bellens, R.; Demanet, J. C.; and Bastenie, P. A. (Hospital St. Pierre, Université Libre de Bruxelles, Bruxelles, France): METABOLIC MODIFICATIONS INDUCED IN THE NORMAL RAT FOLLOWING CHRONIC TREATMENT WITH CORTISONE AND BZ-55. Acta endocrinol. 25:303-11, July 1957.

The paper shows how cortisone acetate, BZ-55, and combined treatment affect glucose assimilation of normal rats during a period of three months. Prolonged treatment with BZ-55 causes a decrease of glucose assimilation but does not modify the gain in weight. Cortisone, on the contrary, promotes an increase of glucose assimilation by the tissues but stops the growth. With combined treatment, BZ-55 plus cortisone, the effect of each separate drug given alone is abolished and glucose assimiliation is restored to a normal level.

Constam, George R. (Zürich, Switzerland): DIFFERENTIAL DIAGNOSIS OF DIABETES MELLITUS. Northwest Med. 56:919-29, August 1957.

The author reviews the various conditions that account for sugar in the urine and that must be considered in the differential diagnosis of diabetes. He suggests that, when diabetes is not present in the case of melituria, paper chromatography offers a simple, cheap and reliable method for identifying the sugar concerned.

Courville, Cyril B. (Los Angeles County Hosp. and Coll. of Med. Evangelists, Los Angeles, Calif.): LATE CEREBRAL CHANGES INCIDENT TO SEVERE HYPOGLYCEMIA (INSULIN SHOCK); THEIR RELATION TO CEREBRAL ANOXIA. A.M.A. Arch. Neurol. & Psychiat. 78:1-14, July 1957.

This study is based upon the residual findings in the brains of two patients who experienced severe degrees of insulin shock through overdosage. A patient thus injured may survive long enough for the changes in the cerebral gray matter to attain a chronic stage. Extensive laminar necrosis of the cortex and destruction of the corpus striatum were present in both cases here reported, as well as diffuse cellular damage in less severely injured zones. These changes, both cellular and architectural, are identical with those alterations residual to severe degrees of cerebral anoxia in cases of carbon monoxide poisoning, nitrous oxide anesthesia, mechanical strangulation, cardiac standstill and prolonged shock. These cases therefore lend support to the theory that insulin shock is but another form (histiotoxic) of cerebral anoxia, with respect to both its general cellular effects and its secondary vasomotor dysfunction.

Croom, J. H.; Duncan, L. J. P.; Dunlop, D. M.; Macgregor, A. G.; and Meiklejohn, A. P. (Royal Infirmary, Edinburgh, Scotland): INSULIN ZINC SUSPENSIONS. Lancet 2:1216-17, Dec. 8, 1956.

The experience with 100 clinic patients showed that less stable diabetics and those with high insulin requirements were better controlled on Protamine Zinc insulin and soluble insulin than on insulin zinc suspensions.

Crowley, Mary F.; Wolff, Frederick W.; and Bloom, Arnold (Whittington Hosp., London, England): TOLBUTAMIDE IN DIABETES: SOME CLINICAL AND BIOCHEMICAL STUDIES. Brit. M. J. 2:327-31, Aug. 10, 1957.

The authors treated forty-two diabetic patients with tolbutamide. These patients were on standard diets, and their diabetes was neither so mild as to be controlled by diet alone nor so severe as to need insulin immediately. Twelve of the forty-two failed to respond and exhibited acetone and elevated blood sugar levels. In twenty-three of the thirty successfully treated patients in whom therapy was carried out for six weeks, relapse did not occur on discontinuation of treatment. In six of seven patients who relapsed following discontinuation of tolbutamide, the drug was successfully reintroduced. Analyses of plasma amino-acid nitrogen and inorganic phosphorus indicate that tolbutamide has a mode of action different from that of insulin. No toxic effects due to tolbutamide were observed in this study.

De Groot, C. A.; and Weber, J. F. (University of Leiden, Leiden, Netherlands): THE INFLUENCE OF GROWTH HORMONE ON CARBOHYDRATE METABOLISM IN DIABETIC RATS. Acta physiol. et pharmacol. neerl. 5:147-53, December 1956.

A single injection of growth hormone in alloxan diabetic rats caused glycogen retention or storage in the liver plus a lowering of blood sugar.

Dimsdale, Lewis J. (Sioux City, Ia.): ORINASE—FOR USE OR ABUSE? J. Iowa M. Soc. 47:576-78, September 1957.

The oral hypoglycemic drug is only an additional adjunct, not a replacement, of other accepted treatments. For the present, careful restriction of cases, according to the limitations herein described, should be continued.

Drury, M. I. (National Maternity Hosp., Dublin, Ireland): INSULIN ZINC SUSPENSIONS. Lancet 2:1358, Dec. 29, 1956.

The results of treatment of 163 diabetics with insulin zinc suspensions. In the majority good control was considered to have been achieved. Satisfactory fetal survival rates in pregnant diabetics were also found.

Dunlop, D. M. (Edinburgh, Scotland): ORAL HYPOGLYCAEMIC COMPOUND. (Correspondence) Brit. M. J. *2*:351, Aug. 10, 1957.

The author comments on his experience with tolbutamide therapy in diabetes mellitus and suggests conservatism in its use.

Editorial: INSULIN ZINC SUSPENSIONS. Lancet *2*:1032-33, Nov. 17, 1956.

This summary of reports to date on the use of insulin zinc suspensions in treatment of diabetes compares the advantages and disadvantages of insulin zinc suspensions with other insulin preparations. The advantages seem to outweigh disadvantages and are: (1) low incidence of allergic reactions (2) a homogeneous series of preparations which may be mixed to provide the variations in timing needs.

Editorial: PREGNANCY, GLYCOSURIA, AND DIABETES. J. Louisiana M. Soc. *109*:384-85, October 1957.

Glycosuria is never trivial, and when it is found in pregnancy the need for proper explanation and appropriate handling is pressing. Glycosuria developing for the first time in a pregnant women is more difficult to interpret than in the nonpregnant individual because pregnancy lowers the renal threshold. Another situation in which the lowering of the renal threshold in pregnancy is of great clinical importance is the production of renal glycosuria in the established diabetic. In this condition, renal glycosuria causes serious difficulty in the management of the diabetes during pregnancy. The criteria for the recognition of diabetes or renal glycosuria, or both, are the same in the pregnant and in the nonpregnant patient.

Editorial: TOLBUTAMIDE IN DIABETES. Brit. M. J. *2*:343-44, Aug. 10, 1957.

The history and present status of tolbutamide therapy in diabetes mellitus are reviewed.

Fagerberg Sven-Erik (Med. Clin., Sahlgrenska Sjukhuset, Gothenburg, Sweden): STUDIES ON THE PATHOGENESIS OF DIABETIC NEUROPATHY. II. RELATION BETWEEN CLINICALLY DEMONSTRABLE NEUROPATHY AND PATHO-ANATOMIC INVESTIGATION OF NERVE. Acta med. scandinav. *156*:295-302, Dec. 31, 1956.

The investigation shows that correlation between clinical diabetic neuropathy and pathological-anatomical examination of the nerve is good. Therefore the case material ought to be very suitable for further studies on the importance of the intraneural vessels in the pathogenesis of diabetic neuropathy. The pathoanatomical picture in the peripheral nerves is completely dominated by myelin sheath degeneration.

Fernández, César; and Brenman, Arnold (Div. of Otolaryngology, University of Chicago, Chicago, Ill.): EFFECT OF HYPOGLYCEMIA ON AUDITORY CORTEX AND COCHLEAR RECEPTOR IN THE CAT. Am. J. Physiol. *188*:249-54, February 1957.

Effect of hypoglycemia induced by insulin and/or functional evisceration on auditory cortex and cochlear responses to sound stimuli was studied in cats. Both responses remained unchanged at blood sugar levels as low as 5 mg. per cent. They diminished in size whenever blood pressure was allowed to fall to low values and returned to nearly normal when it was restored. The observations suggest that carbohydrates are not essential for cochlear function or that the structure contains a large store of them. The presence of responses from auditory cortex during medullary stage of coma suggests that this area does not conform well to the concept of phyletic organization of the central nervous system.

Fisher, Peter (Seattle, Wash.): INSULIN DESENSITIZATION BY AN EASY METHOD. Clin. Med. *4*:463-66, April 1957.

Insulin desensitization, using a single daily dose of long-lasting insulin with gradually increasing dosage, is safe and satisfactory when rapid control is not essential.

Fregly, M. J.; Marshall, N. B.; and Mayer, J. (Dept. of Physiol., Harvard Med. Sch. and Dept. of Nutrition, Harvard Sch. of Public Health, Boston, Mass.): EFFECT OF CHANGES IN AMBIENT TEMPERATURE ON SPONTANEOUS ACTIVITY, FOOD INTAKE AND BODY WEIGHT OF GOLDTHIOGLUCOSE-OBESE AND NONOBESE MICE. Am. J. Physiol. *188*:435-38, March 1957.

Goldthioglucose-obese mice cannot adjust their food intake to meet the increased energy requirements brought on by cold. At all ambient temperatures above 15° C. the spontaneous running activity of these animals is less than that observed for nonobese controls. Activity of obese mice is maximal at 19° C. and minimal at 15° C. or lower. Body weights decrease during exposure to cold. In contrast to that of obese mice, running activity of nonobese controls is maximal at an ambient temperature of 25° C. but nearly ceases at 15° C. or lower. The food intake of these animals increases in the cold and remains elevated even at temperatures at which activity decreases. The body weight of nonobese controls is either maintained constant or increases during exposure to cold air. These experiments suggest that goldthioglucose by its destruction of the ventromedial area of the hypothalamus eliminates the intermediary center through which increased metabolic requirements during cold are translated into additional feeding behavior.

Gutman, Aron; Ziffer, Herman; Gabrilove, J. Lester; and Soffer, Louis J. (Depts. of Medicine and Chemistry, Mount Sinai Hosp., New York, N. Y.): EFFECT OF ORINASE (1-BUTYL-3-PARA-TOLUENE SULFONYLUREA) ON ADRENAL RESPONSE TO CORTICOTROPIN. J. Mt. Sinai Hosp. *24*:516-18, July-August 1957.

Orinase did not cause consistent changes in the levels of plasma and urinary 17-hydroxycorticoids following adrenal cortical stimulation with corticotropin.

Hand, Leo V. (Newton Highlands, Mass.): ANESTHESIA AND SURGERY FOR THE DIABETIC. J. Maine M. A. *48*:351-54, October 1957.

Diabetes, when adequately controlled, does not significantly affect the usual indications for anesthesia. It is to the anesthesiologist's advantage to be familiar with the principles of medical management of the diabetic patient, especially with the various types of insulin that are available and the proper methods of using each, with the diagnostic features that differentiate diabetic acidosis from insulin reaction and with the proper therapeutic measures that each requires. As a rule, indicated surgery for a diabetic patient should be carried out as pomptly as possible. The one exception is the patient who is uncontrolled and therefore "acidotic"; for such a patient treatment of the diabetes almost invariably must be given priority.

Hayes, Daniel W. (Mahorner Clin. and Louisiana State Sch. of Medicine, New Orleans, La.): DIABETES COMPLICATED BY SURGERY. J. Louisiana M. Soc. *109*:358-61, October 1957.

Emergency surgery need never be delayed merely for diabetes, though if acidosis is present a few hours of preparation may be lifesaving. Local, caudal, or spinal anesthetics are the ideal choices, but ethylene and cyclopropane may be used. Ether should not be used in a diabetic patient. Six-hour management during and following surgery makes the fluid and electrolyte problem much easier to handle.

Herold, A. A. (Shreveport, La.): HISTORY OF CONCEPTIONS OF ETIOLOGY AND THERAPY OF DIABETES MELLITUS, PAST AND PRESENT. J. Louisiana M. Soc. *109*:355-57, October 1957.

A brief review of some of the earlier preparations tested for hypoglycemic properties.

Hirayama, Sizuo (Inst. of Physiol., Kumamoto Univ. Coll. of Med., Kumamoto, Japan): STUDIES ON INTERACTION BETWEEN HEART AND PANCREAS TISSUES WITH REGARD TO CARBOHYDRATE METABOLISM. II: INTERACTION IN SUSPENSION FLUIDS OF DIFFERENT KINDS. Kumamoto M. J. *10*:8-11, March 31, 1957.

Interaction between the pancreas and heart tissues with regard to oxygen consumption and lactic acid production was insignificant in the case of glucose-free Ringer's solution while when insulin was added to the glucose-free Ringer, and in the case of glucose-Ringer, interaction was apparent. Mixing of pancreas and heart tissues seemed to increase their oxygen consumption as a whole and decrease the lactic acid production. Decrease of the glucose consumption was marked when the pancreas and heart tissues were mixed.

Homan, J. D. H.; Bouman, J.; Matthijsen, R.; Maske, H.; and Munk, K. (Medizinische Universitatsklinik, München, Germany): DISTRIBUTION OF INSULIN AND ZINC IN DIFFERENT CONSTITUENTS OF THE β-CELLS IN GIANT ISLETS OF PLEURONECTIDAE. Acta physiol. et pharmacol. neerl. *5*:255-56, December 1956.

In histochemical studies, Okamoto observed a relatively high zinc concentration in the islets of the pancreas of mammals, which decreased following a diet rich in carbohydrates. These experiments were extended by Maske and co-workers (1955), who demonstrated a parallel between the zinc concentration in the islets and the availability of insulin therefrom. Zinc was accumulated in the islets of starving animals, whereas large doses of glucose caused a sharp decrease in zinc concentration. On the other hand, injections of zinc-complexing agents, e.g. dithizone, gave rise to permanent diabetes frequently preceded by severe hypoglycemia. Some intermediates of the Krebs' cycle (e.g. citrate) act as zinc-complexing agents. In the presence of sufficient ionic zinc, pure insulin is transformed into a depot form, being sparingly soluble at physiological *p*H, which is reversed by zinc-complexing agents. On this basis, Maske developed theories on a feed-back mechanism for insulin release, whereby glucose metabolism in the islets enhanced by hyperglycemia would provide zinc-complexing intermediates of the Krebs' cycle. In a continued study of the possibility of this mechanism, giant islets of fishes (Pleuronectidae) were homogenized and subjected to fractional centrifugation in two separate experiments, starting from 200 and 500 fresh islets. Nitrogen, zinc, insulin and succinic dehydrogenase were found in the fractions. The insulin and dehydrogenase concentration showed a strict parallel, strongly indicating an accumulation of the bulk of the insulin in the mitochondria fraction. The zinc concentration in this fraction sufficed for a complete precipitation of insulin in neutral systems. The amount of zinc in the microsome fraction was in excess of the binding capacity of the hormone present in this fraction.

Huggett, A. St. G.; and Nixon, D. A. (Univ. of London, and St. Mary's Hosp. Med. Schl., London, England): USE OF GLUCOSE OXIDASE, PEROXIDASE, AND O-DIANISIDINE IN DETERMINATION OF BLOOD AND URINARY GLUCOSE. Lancet *2*:368-70, Aug. 24, 1957.

The authors describe a method applicable to the routine determination of blood glucose, using a mixed enzyme-oxygen acceptor reagent.

Ikkos, Denis; and Luft, Rolf (Dept. of Endocrinology, Serafimerlasarettet, Stockholm, Sweden): ON THE INTRAVENOUS GLUCOSE TOLERANCE TEST. Acta endocrinol. *25*:312-34, July 1957.

The changes in blood glucose concentration during a rapid intravenous glucose tolerance test were studied in fifty tests of nondiabetic subjects and in twenty-two tests of patients with diabetes mellitus, and analyzed statistically. It was found that the changes in blood glucose have the characteristics of a double exponential function of time: One connected with the equilibration of glucose in the extracellular fluid, the other with the removal of glucose by the cells. Similar results were obtained from recalculation of data in the literature. The time for equilibration of glucose was twenty-five to thirty minutes. After this period, a straight-line relationship was obtained when glucose concentration was plotted semilogarithmically against time. From this straight line, the rate of disappearance of glucose can be calculated.

Ikkos, Denis; and Luft, Rolf (Dept. of Endocrinology, Serafimerlasarettet, Stockholm, Sweden): ON THE VOLUME OF DISTRIBUTION OF GLUCOSE IN MAN. Acta endocrinol. *25*:355-44, July 1957.

Measurements of the volume of distribution of glucose were performed in man, using the single injection technic. In fifty-seven instances on forty-eight subjects the volumes of distribution of glucose and insulin were measured simultaneously. In three diabetic subjects the volume of distribution of glucose was measured on two consecutive days, insulin being given intravenously immediately before the second measurement. The results obtained were interpreted as follows: The values obtained for the volume of distribution of glucose by the single injection technic do not necessarily correspond to the true values but are usually only apparent values. In relation to the true volume, the apparent volume of distribution is lower the higher the rate of disappearance of glucose from blood. The true volume of distribution of glucose was calculated to be approximately 40 per cent larger than the volume of distribution of insulin. Diabetics do not differ from nondiabetics with regard to the magnitude of the true volume of distribution of glucose. The values for the true volume of distribution of glucose in man are consistent with the volume of the extracellular compartment.

Kanter, G. S. (Dept. of Physiol., Albany Med. Coll., Albany, N. Y.): HYPOGLYCEMIC EFFECT OF HIGH ENVIRONMENTAL

TEMPERATURE ON DOGS. Am. J. Physiol. *188*:443-46, March 1957.

Exposure of unanesthetized dogs to high environmental temperature (120° F.) and low humidity (<20 per cent) for four hours with no water available for drinking, results in a fall in both whole blood and plasma glucose concentration in spite of the dehydration that also occurs. In one group of dogs so tested the whole blood glucose fell 22 per cent, in another group it fell 16 per cent. The average dehydration was —6 per cent body weight. One would expect such a concomitant dehydration to cause an increase in glucose concentration, much as has been reported in man. Under the experimental conditions imposed, a hypoglycemia resulted in dogs. The hypoglycemia is apparently associated with high temperature, for when the animals were exposed to heat the glucose fell and the rectal temperature increased; when they were removed from heat and allowed to recover, the rectal temperature fell and the glucose returned toward normal. The fall in glucose is metabolic in nature for no evidence of any glycosuria was found. A possible mechanism for the hypoglycemia: More glucose is consumed by the increased exercise of muscles as a result of the panting involved in the effort to maintain body temperature homeostasis.

Katsch, G. (Med. Univ.-Klinik, Greifswald, Germany): DIABETES AND PREGNANCY. München. med. Wchnschr. 99:1108-12, August 1957.

The coincidence of pregnancy and diabetes becomes more and more frequent. From September 1952, until the beginning of 1957, the chief of staff of the gynecological department of the clinic for diabetics performed 157 deliveries in diabetic women; 114 by cesarean section and forty-three by vaginal delivery. The perinatal mortality rate was 19 per cent, and among the last thirty cases only 12.3 per cent. Better results have been achieved by the administration of higher doses of insulin during the last third of pregnancy. The method is described and further problems are outlined. (German)

Keltch, A. K., Krahl, M. E., and Clowes, G. H. A. (Lilly Res. Labs., Indianapolis, Ind.; Marine Biol. Lab., Woods Hole, Mass.; and Dept. of Physiol., University of Chicago, Ill.): ALTERATION BY DINITROCRESOL OF PATHWAYS FOR GLUCOSE OXIDATION IN EGGS OF ARBACIA PUNCTULATA. J. Gen. Physiol. 40:27-35, September 1956.

The $C^{14}O_2$ production by Arbacia eggs and embryos from glucose-1-C^{14}, glucose-2-C^{14}, and glucose-6-C^{14}, has been measured without and with dinitrocresol in the incubation medium. In the absence of the dinitrocresol the CO_2 production from glucose-1-C^{14} is more rapid than from glucose-2-C^{14} and much more rapid than from glucose-6-C^{14}. This, together with previous findings, indicates that glucose is utilized in Arbacia eggs predominantly by way of the hexose monophosphate (TPN) shunt by which the 1-carbon is preferentially converted to CO_2. In the presence of the dinitrocresol, $C^{14}O_2$ from glucose-6-C^{14} approaches that from glucose-1-C^{14}, indicating that, in the presence of this reagent, glucose utilization is diverted from the shunt to the glycolytic pathway. This observation is of interest in relation to the suggestion that various regulatory factors, including hormones, may act in part by diverting metabolites from one pathway to another.

Kinsell, Laurance W. (Moderator) (Inst. for Metabolic Res., Highland Alameda County Hosp., Oakland, Calif.): PANEL DISCUSSION ON DIABETES MELLITUS IN THE AGED. J. Am. Geriatrics Soc. 5:563-81, June 1957.

Comments on aspects of the diabetes problem in the elderly patient.

Kinzer, Charles William; and Tucker, H. St. George (Akron Gen. Hosp., Akron, Ohio; Richmond, Va.): THE ARYLSULFONYLUREA DRUGS WHICH PRODUCE HYPOGLYCEMIA: THEIR USE IN THE TREATMENT OF DIABETES MELLITUS. Virginia M. Month. *84*:455-60, September 1957.

The arylsulfonylureas (carbutamide and tolbutamide) are synthetic drugs related to the sulfonamides. They produce hypoglycemia in normal and certain diabetic subjects. The literature concerning these drugs has been reviewed from the standpoints of mechanism of action, possible side effects, and clinical use.

Landing, Benjamin H. (Children's Hosp. and Children's Hosp. Res. Found., and the Univ. of Cincinnati Coll. of Med., Cincinnati, Ohio): PERI-INSULAR HALOS IN PANCREASES OF DIABETIC CHILDREN. Lab. Invest. 6:458-61, September-October 1957.

Peri-insular halos of large acini, made up of large cells with abundant secretory granules, were found in the pancreas of one of six diabetic children, and in the pancreases of five of a control series of fifty nondiabetic children. The findings suggest that the halos are not caused by diffusion or circulation of insulin to the peri-insular acini, with inhibition of their secretory activity. It cannot be stated whether the halos are caused by glucagon or some other islet secretion or whether they result from removal, by blood passing through the islets, of a factor that stimulates acinar secretion.

Leites, S. M.; Pavlov, G. T.; and Yakusheva, G. S. (All-Union Inst. of Experimental Endocrinology, Moscow, Russia): THE ROLE OF THE CENTRAL NERVOUS SYSTEM IN GLYCAEMIA IN NORMAL AND DIABETIC ANIMALS AFTER REPEATED INTRAVENOUS ADMINISTRATION OF GLUCOSE. Fiziol. Z. *41*:249-56, 1955.

The role of the central nervous system in the control of the blood sugar level was investigated. In experiments on healthy and alloxan diabetic dogs it was shown that repeated intravenous injection of 10 ml. of 50 per cent glucose causes a less marked rise in the blood sugar level than that seen after a single injection. This converse relation between the increase in the blood sugar after repeated injections and the increase after one injection is discussed. It is believed that as a result of summation of stimuli in the vegetative centers controlling the carbohydrate metabolism, a differential inhibition may develop, resulting in a relative predominance of excitation of the parasympathetic centers and thus limiting the increase in blood sugar after repeated injections of glucose. Because glycemia regulation continues when animals are experimentally put under amytal narcosis, the control mechanism may be localized in the lower centers of the central nervous system, most probably in the medulla oblongata. The cerebral cortex exerts a definite influence on this process. (Russian)

Leites, S. M.; and Yakusheva, T. S. (All-Union Inst. of Experimental Endocrinology, Moscow, Russia): THE EFFECT OF THE ADRENOCORTICOTROPHIC HORMONE OF THE PITUITARY AND OF CORTISONE ON GLYCAEMIA, GLYCOSURIA AND KETONAEMIA IN EXPERIMENTAL DIABETES. Probl. Endokr. *1*:47-56, 1955.

ACTH and cortisone in doses which did not give rise to hyper-

glycemia and glycosuria in normal dogs, led to increased hyperglycemia and consequently ketonemia in dogs with alloxan diabetes. Simultaneous administration of ACTH and insulin abolished the hyperketonemic and hyperglycemic effect of ACTH. (Russian)

Leites, S. M.; and Yakusheva, T. S. (Dept. of Pathophysiol. of the All-Union Inst. of Experimental Endocrinology, Moscow, Russia): THE EFFECT OF SUBSTANCES TEMPORARILY INTERRUPTING THE TRANSMISSION OF NERVE IMPULSES IN SYMPATHETIC PATHWAYS ON GLYCOSURIA, GLYCAEMIA AND THE REACTION TO INSULIN, IN EXPERIMENTAL DIABETES. Probl. Endokr. *1*:41-47, 1955.

A single subcutaneous injection of benzoline (1 to 2 mg./kg.) and pachycarpine, i.e., sparteine (10 to 20 mg./kg.), caused diminution of hyperglycemia in dogs with alloxan diabetes. Intramuscular injection of tetraethylammonium iodide had no effect. Injection of pachycarpine and tetraethylammonium iodide increased the reaction to insulin for two hours. Multiple injections (over a period of five to seven days) of benzoline, pathycarpine and tetraethylammonium iodide had no effect on hyperglycemia, but benzoline and pachycarpine produced a slight decrease in diuresis and glucosuria. (Russian)

Lewis, J. G.; and Stephens, P. J. (The Royal Free Hosp., London N.W. 3, England): A RAPID METHOD OF ESTIMATING BLOOD-GLUCOSE RANGES. Lancet *2*:240-41, Aug. 3, 1957.

The authors comment on the use of Clinistix in the detection of glucose in blood, serum, tears and cerebrospinal fluid.

MacDonald, Mary K.; and Bhattacharya, S. K. (Univ. of Edinburgh, Edinburgh, Scotland): HISTOLOGICAL CHANGES IN RATS RENDERED HYPERGLYCAEMIC BY INJECTION OF DEHYDROASCORBIC ACID. Quart. J. Exper. Physiol. *41*:153-61, April 1956.

Rats made hyperglycemic (blood sugar levels of 252 to 500 mg./100 ml.) by repeated intravenous injections of dehydroascorbic acid (DHA) were killed twenty-four hours (Group 1) and four days (Group 2) after the last DHA injection. The pancreas, kidneys, liver, adrenals and thyroid were examined histologically using Gomori's chrome alum hematoxylin and phloxin stain. In Group 1 animals there was degranulation and shrinkage of the beta cells, pyknosis of their nuclei, and occasionally vacuolation of their cytoplasm. Actual disintegration of beta cells was rarely observed. No glycogen was stainable in the beta cells. In Group 2 rats the islets were small; the beta cells were reduced in number, shrunken and usually agranular, with pyknotic nuclei. Cytoplasmic vacuolation was obvious, in part due to glycogen. There was some glycogen deposition in the tubular cells of Group 2 rats, but otherwise the kidneys showed no significant degenerative changes. In the adrenal cortices, a reduction of Sudanophil and Feulgen-positive material was observed in the zona glomerulosa and the zona fasciculata in the males of both groups. No such changes could be demonstrated in the females of Group 2, and no changes were noted in the livers or thyroid of the experimental animals relative to the controls.

Merriam, Joseph C., Jr.; and Sommers, Sheldon C. (Massachusetts Memorial Hosp. and Boston University Sch. of Med., Boston, Mass.): MAMMARY PERIDUCTAL HYALIN IN DIABETIC WOMEN. Lab. Invest. *6*:412-20, September-October 1957.

Among fifty-six autopsied cases of diabetic women, breast sections in twenty (35 per cent) showed peculiar acellular hyaline periductal sheaths, compared to 4 per cent of the controls. Most cases had atrophic breasts, were over sixty years of age, and the staining qualities of the hyalin favored a degenerative lesion. Ultraviolet absorptions of the hyalin were the same as found in intercapillary glomerulosclerosis. The possibility is considered that the mammary hyalin might have been deposited secondary to steroid hormonal stimuli and their withdrawal.

Mosca, Leonardo (Univ. of Cambridge, England, and Univ. of Pavia, Italy): CHANGES IN THE ISLETS OF LANGERHANS ASSOCIATED WITH AGE AND HIBERNATION. Quart. J. Exper. Physiol. *41*:433-41, 1956.

The ratio of alpha to beta cells in rats and bats is at a high level in the young of each of these species. It falls to lower values at about puberty because of an active mitotic multiplication of beta cells. After the adult level of the alpha/beta cell ratio has been reached in bats, carp and tench, it is not affected by changes in the body state arising from hibernation.

Murlin, John R.; and Kramer, Benjamin (Sch. of Med. and Dentistry, Univ. of Rochester, Rochester, N. Y.): A QUEST FOR THE ANTI-DIABETIC HORMONE, 1913-1916. J. Hist. Med. & Allied Sc. *11*:288-98, July 1956.

Experiments performed by the authors long ago, and now presented for the first time in these pages, demonstrated that the pancreatic hormone lowers sugar concentration in the urine of depancreatized dogs and causes a considerably higher respiratory quotient than depancreatized dogs ever exhibit when pancreatic extract is introduced into the stomach. There was no indication of toxicity in these tests.

Nisell, Ove (Dept. of Med., Serafimerlasarettet, Stockholm, Sweden): THE EFFECT OF POSTURE AND INTRAGASTRIC GAS ADMINISTRATION ON THE ORAL GLUCOSE TOLERANCE TEST. Acta med. scandinav. *157*:445-49, June 12, 1957.

Oral glucose tolerance is increased in the strictly supine position and even more so after intragastric administration of carbon dioxide, air or oxygen in that posture. The glucose solution is presumably retarded in its passage from the stomach of a supine subject and the true glucose tolerance is not revealed. Intragastric administration of gas apparently increases this effect. In this investigation intragastric administration of carbon dioxide 50 to 100 cc. per minute, or of oxygen 10 to 20 cc. per minute, for two to three hours, produced no untoward effects.

Novikov, A. T. (Moscow, Russia): TREATMENT OF DIABETES MELLITUS IN PATIENTS WITH CARDIOVASCULAR DISORDERS. Klin. med. (Mosk.) *34*:51-56, 1956.

Coronary circulation of patients with diabetes mellitus, as well as hypertensive disease or coronary atherosclerosis, is not adversely affected when treated with insulin in conjunction with a physiological diet rich in carbohydrates. On the contrary, the removal of diabetic "decompensation" tends to ameliorate the course of hypertensive disease and of the coronary-cardiac affection. It is the hypoglycemia and not insulin as such that is the harmful factor for such patients. To avoid hypoglycemia, administration of insulin in divided doses (three times a day) is recommended, as well as correct distribution of carbohydrate intake and maintenance of sugar in the urine. (Russian)

Petrova, A. N. (Lab. of Physiol. Chemistry, Moscow, Russia): DISTURBANCES OF GLUCOSE ABSORPTION BY LIVER IN ALLOXAN INDUCED DIABETES. Probl. Endokr. *1*:80-85, 1955.

Macerated liver from rabbits with alloxan induced diabetes incubated with glucose showed reduced glucose uptake as compared with controls. Macerated muscle did not show this. Liver slices from healthy and diabetic animals invariably took up glucose on incubation. However, the uptake of glucose was considerably smaller in the case of slices from diabetic animals. (Russian)

Rae, M. V.; and Lewis, R. C. (Shaughnessy Hosp., Vancouver, Canada): ISLET CELL TUMOR IN DIABETES MELLITUS: REPORT OF TWO CASES. Canada M. A. J. 77:691-94, Oct. 1, 1957.

Two cases of islet-cell tumor occurring in diabetes are reported. The first case is that of a fifty-three-year-old white male with diabetes of sixteen-years' duration, who had had marked lability of his diabetes for five years prior to death. He had had frequent severe reactions on minimal insulin therapy. At autopsy an insulinoma was found in addition to specific diabetic renal lesions and severe generalized atherosclerosis. The second case was that of a seventy-two-year-old white male with stable diabetes of recent onset, whose diabetes had been diagnosed when he was hospitalized for complications of peripheral arteriosclerosis. His diabetes was stable and no insulin reactions were noted. At autopsy an insulinoma was found indistinguishable from that of the first case. No insulin assays were reported. The authors conclude that on the basis of clinical behavior the insulinoma in the first case was active while that in the second case was nonfunctioning.

SECOND SYMPOSIUM ON D-860 (TOLBUTAMIDE). Deutsche med. Wchnschr. 82:1513-92, Sept. 6, 1957.

The September 6 issue of the D.M.W. contains the protocol of a second symposium on clinical and experimental studies on the oral antidiabetic agent tolbutamide (D-860, Rastinon, Orinase) by investigators from the Universities of Frankfurt, Freiburg and Munich, the hospitals in Augsburg and Garz, the Institute for Research and Treatment of Diabetes in Karlsburg and the Pharmaceutic Research Department of the Hoechst A.G. (The first symposium had appeared in D.M.W. 81:823-46, 887-906, 1956.) The present symposium is dedicated to Prof. G. Katsch, of Greifswald, the meritorious teacher and investigator in the field of diabetes, in honor of his seventieth birthday.

There seemed to be concurrence by all observers (Creutzfeldt, Mohnike, Pfeiffer, Steigerwald, Stotter and associates) that tolbutamide is a satisfactory agent for the control of diabetic patients with an insulin requirement of less than 30 to 40 units per day, with the exception of the juvenile diabetic. The amount of insulin deficit appears to be far more decisive for the success of oral therapy than age and weight of the patient or duration of the disease. The original contraindications for oral therapy are still maintained: juvenile diabetes, pregnancy and renal insufficiency. After more than two years of wide clinical experience, the side effects of tolbutamide have been gratifyingly rare and the rate of "secondary failure" rather small. No evidence has been found in man for exhaustion of the islets of Langerhans under prolonged tolbutamide therapy. The insulin requirement had remained the same in a group of patients who had been treated successfully with tolbutamide for periods from four to fifteen months and it had not changed in a group of secondary failures who had to be placed back on insulin (Pfeiffer). Yet Mohnike presented evidence of persistent hyperglycemia and glycosuria in a dog after prolonged oral medication. This dog had been pretreated with subdiabetogenic doses of alloxan without manifestation of diabetes, and then received 3 gm. BZ-55 daily for about three months.

Newer experiments seem to support the concept that the sulfonylureas act via stimulation of insulin production or secretion. This was demonstrated by histological changes in the β-cells (Bänder, Pfeiffer, Steigerwald, Creutzfeldt) and by metabolic studies. With regard to morphologic changes, it was emphasized that these vary in various animal species. In the rat and the calf a significant decrease of β-cell granulation was demonstrated at the beginning of treatment, with a gradual return to normal appearance with continuing therapy; normal values are, however, only seldom attained. In the rabbit only prolonged treatment seemed to cause significant degranulation. New formation of islet cells or hyperplasia of islets has as yet been seen only in the rat (Baender). Most suggestive for the insulin-stimulating mechanism are the data from the Frankfurt group (Pfeiffer, Steigerwald and associates). In short- and long-term experiments on calves a correlation was established between changes in blood sugar, pancreatic insulin content and islet cell morphology. Moreover, Steigerwald and associates presented clinical observations indicating that the sulfonylureas, like insulin, cause a rise in lactic and pyruvic acid accompanying the hypoglycemia. These data, if confirmed, would go far to prove an insulin-like mechanism and an effect on peripheral glucose utilization. They are, however, still in disagreement with the observations of American investigators. There were other experimental data which still do not quite fit into the insulin concept. Thus, Creutzfeldt emphasized, for instance, the failure of the sulfonylureas to cause (a) glycogen deposition in the diaphragm (b) a change in the arteriovenous blood sugar difference and (c) a more severe hypoglycemia in the hypophysectomized animal than insulin does. Moreover, Wallenfels and Creutzfeldt report studies on liver enzymes that seem to demonstrate significant differences in the action of insulin and the sulfonylureas.

The summary of the symposium proposes a dualistic theory of action of tolbutamide: It is thought to cause a release of insulin from the beta cells of the islets of Langerhans and at the same time to affect certain enzymatic metabolic reactions. In the normal individual and a specific group of diabetics, the metabolic effects are thought to result from an interplay of these mechanisms of action. The extrapancreatic metabolic changes in themselves do not suffice to produce hypoglycemia. For the hypoglycemic reaction, the responsiveness of pancreatic insulin production or release is a prerequisite.

Various concepts were presented about this increased responsiveness of the insulin release mechanism:

1. Tolbutamide causes an increased insulin release by a direct or indirect (enzymes, metabolites?) action (Mohnike).

2. Tolbutamide may sensitize the "cell receptors" responsible for the insulin release; and thus this system may function at a lower level (Bänder).

3. The sulfonylurea derivatives primarily cause a release of active insulin, which exists in the beta cells in soluble form. This is followed by a mobilization of the depot form of insulin, which is bound to the granules. This process is dependent on a rising blood sugar concentration and repeats it-

self in the same way after each administration of a sulfonylurea derivative (Pfeiffer).

4. The sulfonylurea derivatives react with insulin in the beta cells. The resulting combination of insulin-sulfonylurea can no longer be stored within the islets and attaches itself particularly firmly to certain points in the liver. The formation of an insulin-sulfonylurea complex in the beta cells would explain the changed morphology of the beta cells, as well as the necessary presence of beta cells for the sulfonylurea derivatives to be effective. It would also explain the various effects of these drugs on the liver, even in low concentrations, which do not resemble the effects of insulin on this organ (Creutzfeldt).

5. A chemical mechanism for the increased release of insulin may lie in a direct reaction of the sulfonylureas within the islets or an indirect reaction through a metabolic product that has been formed in greater than normal amounts by the action of the sulfonylureas in the liver or the islets (Wallenfels). (German)

Seegers, Winnifred; McGavack, Thomas H.; Harr, Helmut O.; Erk, Vernon O.; and Spellen, Bruce (New York Med. Coll., Bird S. Coler Hosp., Welfare Island, New York): INFLUENCE OF THE ARYLSULFONYLUREAS ON THYROID FUNCTION IN OLDER DIABETIC MEN AND WOMEN. J. Am. Geriatrics Soc. 5:739-46, August 1957.

Thyroid function was studied in fifty-five elderly patients with diabetes mellitus before and during treatment with the sulfonylureas, carbutamide and tolbutamide. No clear-cut clinical evidence of hypothyroidism was observed in any patient at any level of dosage used. Large doses of carbutamide (3 and 4 gm. daily) for four days depressed the uptake of radioiodine by the thyroid gland. No change in uptake was observed when tolbutamide was used in similar dosage for the same length of time. The long continued use of either sulfonylurea in a dosage of 1 gm. daily was not associated with any appreciable change in the thyroidal uptake of radioiodine. However, in the case of carbutamide, when the dosage was increased to 2 gm. daily, there was a statistically significant depression of the radioiodine uptake.

Silver, A. A.; and Shaw, Helen M. (Sinai Hosp. of Baltimore, Inc., Baltimore, Md.): TOWARD FURTHER SIMPLIFICATION OF THE DIABETIC DIET. Sinai Hosp. J. 6:99-101, April 1957.

Changes have been made that have solved many problems in instructing patients. An attempt to eliminate every possibility of misunderstanding on the part of the patients is made and it is used as an introduction to a diabetic dietary regimen. In the authors' "Food Substitution List" they have eliminated the milk exchange list and the fat exchange list, because of the use of minimum-fat diets (i.e. minimum free fat and only skim milk products). Values in the food substitution list have not been altered from the original exchange list. The amount of time necessary to explain the diet to patients and to make it understandable has been considerably diminished. Patients achieve better understanding of their diets, follow them more closely and achieve better diabetic control.

Silver, A. A.; and Zeligman, Israel (Baltimore, Md.): NECROBIOSIS LIPOIDICA DIABETICORUM CONTROLLED EQUALLY BY INSULIN AND TOLBUTAMIDE (ORINASE). Sinai Hosp. J. 6: 106-09, April 1957.

A case is reported of true necrobiosis lipoidica diabeticorum which disappeared with good diabetic control with insulin and tolbutamide and which recurred with decontrol of the diabetes. Treatment in this case does not support previous statements that "control of the diabetic state does not benefit the lesion."

Skouby, Arne P. (Med. Out-Patient Clin., University Hosp., Copenhagen, Denmark): VASCULAR LESIONS IN DIABETICS: WITH A SPECIAL REFERENCE TO THE INFLUENCE OF TREATMENT. Med. Scandinav. *155*: (Suppl. 317) 1-46, 1956.

Factors influencing the development of late complications are studied in diabetics with an onset of the disease before the age of forty by reviewing the pertinent literature and by analyzing a series of 286 diabetics with an onset of the disease between 1924-1954 who were prescribed at random either the classical diet or the so-called free diet without sugar.

Sex and severity of diabetes have no correlation with the incidence of late lesions, in ageement with previous studies. The age at the onset of diabetes is of no influence on the incidence of retinopathy, while patients with an onset of the disease between twenty and thirty years of age seem to develop nephropathy less frequently than other patients.

The degree of medical control is of dominant importance for the incidence of late lesions. This is demonstrated conclusively by the results obtained when the present series is grouped according to the time of onset (diabetes duration), the degree of adjustment and according to the type of treatment prescribed. When the series was divided according to the type of diet prescribed a significantly higher incidence of late lesions and of inadequate medical adjustment was found in patients on the free diet. Most of the patients with no or little glucosuria were on the classical diet demonstrating that in the present material the average degree of adjustment obtained on the classical diet surpassed that obtained when the free diet without sugar was used.

Splitter, S.; Brown, F. R., Jr.; Friskey, R. W.; Grindle, L.; and Kinsell, L. W. (Dept. of Med., and the Inst. for Metabolic Res., Highland Alameda County Hosp., Oakland, Calif.): TREATMENT OF DIABETIC PATIENTS: OBSERVATIONS ON THE USE OF CARBUTAMIDE AND TOLBUTAMIDE. California Med. *85*: 285-88, November 1956.

A group of thirty-two patients were slowly taken off insulin, and a sulfonamide preparation was given following discontinuance of insulin. Ketonuria developed in one patient only after discontinuing insulin. Eighty-one per cent of the patients showed a significant response to the sulfonamides, with only one patient showing any toxic effect, a drop in leukocyte count. There was no obvious correlation between presence of obesity and response to sulfonamides or to duration of diabetes. Only one responsive patient was less than thirty-eight years of age.

Stahl, J.; and Dorner, M. (Clinique Medicale B, Strasbourg, France): GLUCAGON RESEARCH: IN REFERENCE TO THE ORIGIN OF GLUCAGON IN THE DOG PANCREAS. Rev. franç. etudes cliniques et biologiques 2:26-43, January 1957.

Extracts of normal dog pancreas injected into a normal dog cause a transient hyperglycemia due to glucagon, which has a peak at about nine minutes after injection. The hyperglycemia is followed by insulin hypoglycemia. Glucagon is not destroyed by various steps known to inactivate insulin. Glucagon is still found in extracts from pancreas in which the acini are sclerosed following ligature of the pancreatic duct. This is also the case in extracts after the destruction of the beta

cells in the islets of Langerhans by alloxan or after their atrophy induced by anterior pituitary extract injections. Repeated injections of anterior pituitary extracts, giving rise to "young" diabetes, cause an increase in the size and number of the alpha cells, with hypergranulation in their protoplasm. Extracts of such pancreas have a greater and longer lasting hyperglycemic effect than that from normal pancreas.

Substances which cause a lesion, with diminished granulation, of the alpha cells in dogs, such as cobalt chloride and Synthalin A, result in a smaller hyperglycemic effect of pancreatic extracts from animals so treated. The pancreas of a hypophysectomized dog removed some hours after the death of the animal contained no histologically recognizable alpha cells. An extract of this pancreas showed no hyperglycemic activity.

In the author's experience there has been a fairly direct relationship between the hyperglycemic effect of pancreatic extract and the number and histological appearance of the alpha cells. It is thought that the findings are strongly in favor of glucagon formation by the alpha cells of the pancreas.

Surtshin, A.; Cordonnier, James K.; and Lang, S. (Dept. of Physiol., Washington Univ. Sch. of Med. and Jewish Hosp., St. Louis, Mo.): LACK OF INFLUENCE OF THE SYMPATHETIC NERVOUS SYSTEM ON THE CALORIGENIC RESPONSE TO THYROXINE. Am. J. Physiol. *188*:503-06, March 1957.

Normal rats as well as thyroparathyroidectomized rats concurrently given thyroxine and an adrenergic blocking dose of Dibenzyline show the expected rise in rate of oxygen consumption. After bilateral adrenal demedullation the resting rate of oxygen consumption is not significantly different from normal, and injection of a large dose of thyroxine either with or without concurrent administration of adrenergic blocking doses of Dibenzyline is followed by a significant rise in the rate of oxygen consumption. Our data and other pertinent published data lend support neither to the claim that the calorigenic effect of exogenous thyroxine is dependent upon the presence of normally acting adrenal medullary hormones nor to the claim that the metabolic changes of thyrotoxicosis are due to the physiological effects of epinephrine and norepinephrine as augmented by the thyroid hormones.

Tunbridge, R. E.; and Paley, R. G. (Univ. Dept. of Med. Genl. Infirmary, Leeds, England): INSULIN ZINC SUSPENSIONS. Lancet 2:1161, Dec. 1, 1956.

Presents the experience with insulin zinc suspensions in 203 patients over a three-year period. The conclusion drawn is that insulin zinc suspensions show no special advantages over the other insulins in the treatment of unstable diabetics.

Veller, N. S.; Genes, S. G.; Radkina, B. S.; and Charnaya, P. M. (Ukranian Inst. of Experimental Endocrinology, Kharkov, Russia): THE ROLE OF THE NERVOUS SYSTEM IN THE DEVELOPMENT OF DIABETES MELLITUS. Probl. Endokr. *1*:77-84, 1955.

The authors suggest that hyperglycemia in diabetes mellitus is a compensatory reaction. Deficiency of insulin leads to diminished carbohydrate assimilation by the tissues, including cerebral tissue. It is the latter that mobilizes the adaptation mechanisms. Sympathetic stimulation and increased secretion of adrenalin create hyperglycemia, which enhances the ability of the tissues to assimilate carbohydrates. (Russian)

Walker, G.; Slater, J. D. H.; Westlake, E. K.; and Nabarro, J. D. N. (Diabetic Clinic, the Middlesex Hosp., London, England): CLINICAL EXPERIENCE WITH TOLBUTAMIDE. Brit. Med. J. 2:323-25, Aug. 10, 1957.

The authors studied seventy-two patients treated with tolbutamide for up to one year and felt that about 50 per cent of patients with mild diabetes that cannot be controlled by diet alone will benefit from this type of therapy. It should be given only to adults who are not excessively overweight, whose diabetes cannot be controlled by diet alone, and who do not become ketotic even when untreated. The response may be evident immediately, or only after several weeks. Increasing weight in patients was often associated with decreasing effectiveness of the drug.

Walker, Joan B. (Diabetic Dept., Leicester Royal Infirmary, Leicester, England): STRESS AND DIABETES. Practitioner *178*: 590-99, May 1957.

On clinical, statistical and experimental evidence all forms of stress play an important part in the disturbance of good control in diabetes. The effect of emotional stress, usually anxiety, is apparent in the older group of mild, obese, insulin-resistant cases. In the younger group of acute, thin, insulin-sensitive diabetics, stress due to associated endocrine imbalance is more common. It is probable that emotional stress is never the sole etiological agent in diabetes, but may have an additive or precipitating effect. As no single diabetogenic hormone has yet been isolated it is assumed that the mechanism is under hypothalamic control and may be in the nature of an overflow from adrenocorticotrophic, gonadotrophic and thyrotrophic hormones stimulating the growth hormone. A plea is made for the management of certain categories of diabetics in special units where the staff can become interested and competent to care for them in such a way as to give maximum security, education and encouragement.

Wallbank, W. L. (William Roche Memorial Hosp., Toledo, Ohio): DIABETES AND TUBERCULOSIS. Ohio M. J. 53:920-21, August 1957.

Although the outlook for the patient who suffers from both diabetes and tuberculosis has been regarded as exceedingly gloomy in the past, under modern treatment of both diseases the prognosis is favorable. As for tuberculosis alone, the results in carefully controlled diabetics are almost as favorable as those in the nondiabetic.

Weisenfeld, Shirley; Jauregui, Raul Hernandez; and Goldner, Martin G. (Dept. of Medicine, Jewish Chronic Disease Hospital, Brooklyn, and State University of New York Medical Center, New York City): INACTIVATION OF INSULIN BY THE ISOLATED LIVER OF THE BULLFROG. Am. J. Physiol. *188*:45-48, January 1957.

Experiments are presented in which insulin solutions were perfused through isolated frog livers in order to study the inactivation of this hormone by liver tissue. The solutions were many times recirculated, and aliquots were tested biologically at various intervals for hypoglycemic activity. While insulin retains its activity after a single frog liver perfusion, it is gradually inactivated with increasing numbers of re-perfusions. This result is in accord with the inactivation of insulin by liver slices and liver brei as reported by others. The relatively slow inactivation of insulin, when perfused through the isolated frog liver, is in contrast to the inactivation of glucagon which,

as previously reported, loses its hyperglycemic activity after a single perfusion through this preparation. This difference in rates of inactivation of insulin and of glucagon suggests that the inactivation is catalyzed either by two different enzyme systems or by a single enzyme system which acts at different rates upon different substrates. The relatively slower inactivation of insulin by the liver may reflect its widespread extrahepatic as well as hepatic effects in distinction to glucagon whose action is largely limited to the liver.

Wells, Benjamin B. (Creighton Univ. Sch. of Med., Omaha, Neb.): THE VASCULAR COMPLICATIONS OF DIABETES. Nebraska M. J. *41*:424-27, November 1956.

Some of the current concepts of vascular lesions associated with diabetes are summarized, and a few of the theories that are being followed by investigators in this field are outlined.

Wendland, John P. (Minneapolis, Minn.): THE EYE IN DIABETES MELLITUS. Minnesota Med. 39:781-84, December 1956.

The retinopathy of diabetes is dependent upon venous and capillary changes in the retina, not upon arteriolar alterations. The changes in the kidney glomeruli and the retina represent the same pathologic process and thus probably share a common etiology. The prevention and cure of the damage to the eyes caused by diabetes is not yet at hand. With a disease so chronic and with spontaneous remissions, one must view all new treatments with extreme skepticism. However, a constant search for the solution to so serious a problem must be relentlessly pursued through a combination of basic research and clinical evaluation. There is no place for hardening of the categories in the study of this disease.

Wheelock, Frank C., Jr.; McKittrick, John B.; and Root, Howard F. (New England Deaconess Hosp., Boston, Mass.): EVALUATION OF TRANSMETATARSAL AMPUTATION IN PATIENTS WITH DIABETES MELLITUS. Surgery *41*:184-89, February 1957.

Of sixty-seven patients who had transmetatarsal amputation for neuropathy or infection, only five required reamputation subsequently. Of 366 patients who had transmetatarsal amputation for arterial insufficiency, approximately one-third failed. The incidence of failure was closely related to the evaluation of collateral circulation by venous filling time and other indices. Approximately 61 per cent of those living three years after operation had healed stumps; approximately 50 per cent of those living five years after operation had healed stumps.

Whitehouse, Fred W.; Lowrie, William L.; and Hodgkinson, C. Paul (Depts. of Med. and Obst., Henry Ford Hosp., Detroit, Mich.): DIABETES AND PREGNANCY. J. Michigan M. Soc. 55:1211-17, October 1956.

Sixty-one pregnancies in forty diabetic mothers have been reviewed. There was a fetal salvage of 68.8 per cent in this series. The incidence of pre-eclampsia is 37.7 per cent; polyhydramnios, 20 per cent; ketoacidosis, 19.7 per cent. The fetal survival was adversely affected by the last but not by the first two. Early timed delivery has been practiced during the time covered by this study. The over-all fetal survival with the use of cesarean section is 88 per cent.

Whitehouse, Fred W.; and Root, Howard F. (Henry Ford Hosp., Detroit, Mich.; Joslin Clin. and New England Deaconess Hosp., Boston, Mass.): NECROTIZING RENAL PAPILLITIS AND DIABETES MELLITUS. J. A. M. A. *162*:444-47, Sept. 29, 1956.

In a group of 14,252 diabetics, eleven cases of necrotizing renal papillitis were found. Four patients showed close clinicopathologic correlation; in seven, the disease seemed to be an incidental pathologic finding. Evidence of infection and renal failure was prominent in the patients with symptomatic necrotizing renal papillitis, but oliguria and anuria were unusual. Of the eleven cases, eight were unilateral. Ten patients died, and one was cured of nephrectomy. Measures for the prevention of papillitis should include prevention and vigorous treatment of urinary tract infections, eradication of obstructive uropathy, and good control of diabetes. It should be recognized that necrotizing renal papillitis is not uncommon in diabetic patients and should be suspected if sepsis or progressive renal failure exists.

Whitney, J. E.; and Young, F. G. (Schl. of Med., Univ. of Arkansas, Little Rock, Ark.; Dept. Biochem., Univ. of Cambridge, London, England): SOME HORMONAL INFLUENCES ON THE GLUCOSE UPTAKE OF NORMAL RAT DIAPHRAGM IN VITRO. Biochem. J. 66:648-51, August 1957.

When normal rat diaphragm is incubated with serum from hypophysectomized diabetic rats the glucose uptake is: (a) greater than in diaphragm in the presence of serum from diabetic rats; (b) similar to uptake of diaphragm incubated with serum from hypophysectomized diabetic rats treated with either growth hormone or cortisone; (c) greater than when serum was used from hypophysectomized diabetic rats treated with growth hormone and cortisone simultaneously. When normal rat diaphragm is incubated with serum from normal rats treated with growth hormone and cortisone simultaneously for fourteen days, the glucose uptake in vitro is slightly but significantly lower than that observed with diaphragm in normal rat serum. These results are compatible with the view that there is present in the serum of diabetic rats an inhibitor of glucose uptake by diaphragm tissue, the presence of which depends upon the availability of both growth hormone and cortisone or related substances. This inhibitor can appear in the serum of the normal rat treated with both growth hormone and cortisone.

Whitney, J. E.; and Young, F. G. (Schl. of Med., Univ. of Arkansas, Little Rock, Ark.; Dept. Biochem., Univ. of Cambridge, London, England): THE INFLUENCE OF INTRAVENOUS GLUCOSE ON BLOOD-INSULIN ACTIVITY IN THE RAT. Biochem. J. 66:645-48, August 1957.

The authors measured the insulin-like activity of plasma from rats given glucose intravenously by use of the rat diaphragm method. The activity was lower than normal for thirty minutes after the injection of glucose and then rose above normal. The glucose uptake of diaphragm obtained from the glucose injected rats was simultaneously examined by incubation in glucose containing buffer. The glucose uptake first rose and then fell below normal. The authors suggested, as a possible interpretation, that when the blood glucose rises, insulin leaves the plasma and becomes bound to the tissues of the diaphragm, where it exerts a physiological effect.

Young, F. G. (University of Cambridge, Cambridge, England): CLAUDE BERNARD AND THE DISCOVERY OF GLYCOGEN: A CENTURY OF RETROSPECT. Brit. M. J. *1*:1431-37, June 22, 1957.

The work of Claude Bernard in the field of carbohydrate metabolism is discussed, with particular reference to the discovery of glycogen and the present problems associated with the investigation of glycogen storage disease.

ORGANIZATION SECTION

OFFICERS AND MEMBERS OF COUNCIL, AMERICAN DIABETES ASSOCIATION, 1957-1958

HONORARY PRESIDENT, ELLIOTT P. JOSLIN, M.D., *Boston*

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HENRY B. MULHOLLAND, M.D., *Charlottesville, Va.;*
HENRY T. RICKETTS, M.D., *Chicago;* FREDERICK W. WILLIAMS, M.D., *New York*

EIGHTEENTH ANNUAL MEETING JUNE 21-22, 1958

Attention of ADA members and readers of DIABETES is called to the rescheduling of the first Scientific Session of the Eighteenth Annual Meeting from the afternoon to the morning of Saturday, June 21, 1958. As previously announced, the Scientific Sessions will be held Saturday and Sunday, June 21-22, at the Hotel Mark Hopkins, in San Francisco, California.

The following meetings have been arranged for Saturday, June 21:

9 a.m.—1 p.m.	Scientific Session (Banting Memorial Lecture, 11 a.m.—12 noon)
12:30 p.m.—1:30 p.m.	Luncheon for Lay Delegates
1:30 p.m.—3:00 p.m.	Assembly of Delegates
3:30 p.m.—5:00 p.m.	Board of State Governors
3:30 p.m.—5:00 p.m.	Special Program for Lay Delegates
6:30 p.m.—7:30 p.m.	Social Hour
7:30 p.m.	Banquet

The foregoing schedule was arranged after careful consideration of The Endocrine Society's program to prevent as much conflict as possible, and to allow time for most of the members of the Association to attend The Endocrine Society's panel on "Clinical Treatment of Diabetes" from 3:30 to 5 p.m. In addition, the program of The Endocrine Society on Friday afternoon, June 20, will be on "Diabetes and Metabolism." American Diabetes Association members are invited to attend these sessions of The Endocrine Society without paying a registration fee, providing they present the ADA registration badge at the time of admission. In turn, members of The Endocrine Society will be admitted to the Scientific Sessions of the American Diabetes Association without charge by registering at the ADA desk.

A copy of the Program, containing abstracts of papers, will be sent to each member without charge. Additional copies of the final Program may be secured at a cost of $1.00 each. Nonmembers also may obtain a copy at the same price by requesting one from the American Diabetes Association, Inc., 1 E. 45th St., New York 17, N.Y.

SEVENTH POSTGRADUATE COURSE

The American Diabetes Association will hold its Seventh Postgraduate Course in Diabetes and Basic Metabolic Problems Jan. 21, 22 and 23, 1959, in St. Louis, Missouri. William H. Olmsted, M.D., St. Louis, will serve as Director, with Henry E. Oppenheimer, M.D., St. Louis, Co-Director. The Postgraduate Course series of the Association, which is developed by its Committee on Professional Education, is open to members of the medical profession.

1958 LILLY AWARD TO JAMES B. FIELD

James B. Field, M.D., of the National Institute of Arthritis and Metabolic Diseases, Bethesda, Maryland, will be presented with the 1958 (second) Lilly Award at the Eighteenth Annual Meeting of the American Diabetes Association June 21-22, 1958, in San Francisco. The annual Award, supported by Eli Lilly and Company, consists of $1,000 and a medal. Its purpose is to recognize demonstrated research in the field of diabetes, taking into consideration independence of thought and originality. Dr. Field is currently engaged in postdoctoral studies in London, England.

ADA AWARDS RESEARCH FELLOWSHIPS

The Committee on Research and Fellowships of the American Diabetes Association announces the renewal, for the 1958-59 academic year (July 1, 1958—June 30, 1959), of the following three Research Fellowships:

Wilson Randolph Tucker, M.D., Cincinnati, Ohio, for the study of experimental production of vascular lesions in the retina by administration of corticotropin or adrenal steroids, and the possible role of hyperadrenalism and hyperlipemia in the genesis of such lesions. Dr. Tucker will continue to work with Chester Coggeshall, M.D., Chief, 1st Medical Service, St. Luke's Hospital, and Edwin F. Hirsch, M.D., Professor Emeritus of Pathology, University of Chicago, Chicago, Illinois.

Jefferson Earle White, Jr., M.D., Atlanta, Georgia, for the study of rate of utilization of ketone bodies (ketolysis) in the rat in varying states of endocrine and metabolic imbalance. Dr. White will continue to work with Frank L. Engel, M.D., Professor of Medicine, Assistant Professor of Physiology, Director, Division of Endocrinology, Duke University School of Medicine, Durham, North Carolina.

Albert I. Winegrad, M.D., Philadelphia, Pennsylvania, for the study of the effect of various hexoses on unesterified fatty acids in plasma and in adipose tissue, in normals and in diabetics. He will continue to work with Francis D. W. Lukens, M.D., The George S. Cox Medical Research Institute, Hospital of the University of Pennsylvania, Philadelphia, Pennsylvania.

Adler Foundation Research Fellowship. David Norman of Shrewsbury, Massachusetts, has been awarded the three-year Adler Foundation Research Fellowship, to begin with the 1958-59 academic year. He will work on the action of insulin on the rat diaphragm under a variety of conditions. The research will be conducted the first year under the direction of Dr. William A. Hiestand, Professor of Physiology, Purdue University, West Lafayette, Indiana, and the remaining two years with Dr. Oscar Hechter, Worcester Foundation for Experimental Biology, Shrewsbury, Massachusetts.

The Committee on Research and Fellowships plans to award at least one Fellowship for the academic year 1959-60. The deadline for applications is Nov. 15, 1958. Requests for application forms and other inquiries should be addressed to Mr. J. Richard Connelly, Executive Director, who will forward the information to the Committee.

APRIL 1 DEADLINE FOR SIXTH MEDICAL STUDENT-INTERN ESSAY CONTEST

Medical students, interns and physicians within two years after their graduation from medical school must submit their entries in the 1957-58 Medical Student-Intern Essay Contest by April 1, 1958. Entrants should submit the original and two copies of their manuscripts. Manuscripts should be typewritten, double-spaced, and mailed to: Committee on Scientific Awards, American Diabetes Association, Inc., 1 East 45th St., New York 17, N.Y. Any subject related to diabetes and basic metabolic problems may be selected.

The author of the best paper reporting original work, whether laboratory investigation or clinical observation, will receive an award of $250. This prize is again made possible by the St. Louis Diabetes Association.

For the best review article or case report the author(s) will be awarded a prize of $50.

Papers will be judged on the basis of value of the material and method of presentation.

Members of the American Diabetes Association and subscribers to DIABETES are asked to encourage medical students and interns to enter the contest.

THIRD IDF CONGRESS AT DÜSSELDORF

Howard F. Root, M.D., of Boston, Vice President of the International Diabetes Federation, has announced that some space is still available on the plane which has been chartered for the convenience of those who would like to attend the Third Congress of the Federation at Düsseldorf, Germany, July 21-25, 1958.

Members of the American Diabetes Association and its Affiliates have been invited to book passage on a chartered Air France plane to Düsseldorf at $179.75, or about half the regular one-way rate. The offer also extends to members of their immediate families.

The plane will leave New York for Boston on July 19 at 1 p.m., arriving in Boston at 2 p.m. It will leave Boston at 3 p.m., arriving in Düsseldorf the next morning (July 20) at about 8 a.m.

Copies of the IDF brochure which includes the tentative program and details concerning reservations at the Congress are available at the office of the American Diabetes Association upon request. Visits to points of interest in and around Düsseldorf have been planned and social activities are being arranged for the ladies.

Inquiries regarding reservations on the chartered plane should be addressed promptly to the Manning Travel Bureau, Hotel Kenmore, Boston 15, Massachusetts. A $50.00 deposit should accompany requests for reservations.

NEW SCIENTIFIC EXHIBIT

A new exhibit entitled "Diabetes—Today and Tomorrow" will be shown for the first time at the American Medical Association Annual Meeting, June 23-27, 1958, in San Francisco, California. The exhibit was developed by the Committee on Scientific Exhibits of the American Diabetes Association: Marshall I. Hewitt, M.D., Chairman; DeWitt E. DeLawter, M.D., William R. Kirtley, M.D., Howard F. Root, M.D., and George F. Schmitt, M.D.

The exhibit will consist of the following panels: (1) "Employment of the Diabetic," showing his present status in industry; (2) "Diet," relating specifically to changes in carbohydrate, protein and fat content; and (3) "Hypoglycemic Agents," both oral and parenteral. The subject matter will focus attention on proposed suggestions for diabetes tomorrow against a backdrop of the present status of diabetes in each of the three selected areas.

Approximately a year after its initial display, this exhibit will be added to the scientific exhibits already available on a loan basis to Clinical Societies of Affiliate Associations and to other medical organizations. These exhibits are as follows: "Pathology of Diabetes," "Management of Diabetes Mellitus," "Vascular Complications of Diabetes," and "Diabetes Detection by the Physician."

SUMMER CAMP LIST IN *ADA FORECAST*

Members of the American Diabetes Association and readers of the Journal will be interested to know that an up-to-date list of summer camps for diabetic children, containing detailed information about each camp, will be published in the May-June 1958 issue of the ADA FORECAST. A map showing geographical locations will also be included. Single copies of the magazine or a reprint of the article will be available on request.

DIABETES WEEK, 1958

The week of November 16-22 will be observed as Diabetes Week. Each year the week which precedes Thanksgiving is the official Diabetes Week as selected by the Council upon recommendation of the Executive Committee. Affiliate Associations and Committees on Diabetes Detection of County and State Medical Societies are urged to note these dates in making plans for development of Public Education and Detection programs.

AFFILIATE ASSOCIATION ACTIVITIES

Many meetings of Lay Societies of Affiliates of the American Diabetes Association are announced in every issue of the ADA FORECAST. A cordial invitation is extended to FORECAST readers, all diabetics and their friends to attend these meetings for the purpose of becoming better informed about diabetes. Physicians may wish to call the attention of their patients to the fact that the dates and places of these meetings are published in FORECAST.

NEW SUPPLEMENT TO MEMBERSHIP DIRECTORY

A supplement to the 1954 Membership Directory will be mailed to all members of the American Diabetes Association on or about March 15, 1958. This supplement includes the names of all members elected from May 2, 1954, through Oct. 31, 1957.

Members who wish to replace their 1954 Membership Directory may secure a copy at a cost of $1.00 by addressing their requests to the American Diabetes Association, Inc., 1 East 45th St., New York 17, N.Y.

QUANTITY PRICES FOR *FACTS ABOUT DIABETES*

FACTS ABOUT DIABETES, the thirty-two page booklet published by the American Diabetes Association, offers invaluable information about diabetes both for the diabetic and the non-diabetic. Many physicians, clinic and hospital staffs use this booklet to supplement their instructions.

To aid those who wish to furnish booklets to classes and to new patients, the following prices have been established, offering a reduction in cost for purchase in quantity:

1-99 copies, $.25 each; 100-249 copies, $.20 each; 250-499 copies, $.195 each; 500-999 copies, $.1875 each; 1,000 copies and over, $.175 each. Order blanks are available upon request to the American Diabetes Association, Inc., 1 East 45th St., New York 17, N.Y.

DIABETES ABSTRACTS

A limited number of back issues of DIABETES ABSTRACTS are available without charge upon request to the American Diabetes Association, 1 East 45th St., New York 17, N.Y. These issues include: Volume 5, Number 4 (October 1946), which contains the five-year cumulative index for Volumes 1-5; Volume 10, Number 1 (January 1951); and Volume 4, Number 3 (July 1945).

STUDENT SUBSCRIPTION RATES

Medical Students, Interns and Residents are offered a subscription to DIABETES at a special price of $4.50 per year, half of the regular subscription rate.

BINDERS FOR VOLUME 7 NOW AVAILABLE

A binder for 1958 matching those for Volumes 1, 2, 3, 4, 5 and 6 (1952-57 issues) of DIABETES is available for immediate shipment at a price of $2.25. This insert binder is sturdy and attractive and will hold six issues of the magazine, plus the index supplement. Binders for Volumes 1, 2, 3, 4, 5 and 6 also are available at the same price. Address your orders to American Diabetes Association, Inc., 1 East 45th St., New York 17, N.Y.

NEW MEMBERS

Active

The following were elected as of Feb. 1, 1958, and March 1, 1958:

Alabama	
Goodman, Seaburt	Birmingham
Gordon, Eugene W.	Oneonta
Herren, Wood	Birmingham
Hunt, Marcus C.	Fairfax
Arizona	
Kohl, Harold W.	Tucson
California	
Burton, Stanley D.	San Francisco
Florida	
Langer, Edward M.	Sarasota
Georgia	
Bradley, William J., III	Woodbury
Brill, Harry H.	Columbus
Evans, Edwin C.	Atlanta
Roche, William P., Jr.	Dublin
Tarplee, Scott L.	Atlanta
Wolff, Bernard P.	Atlanta
Idaho	
Rees, Milton T.	Idaho Falls
Kentucky	
Willard, John H.	Harlan
Louisiana	
Wilson, James W., Jr.	Shreveport
Massachusetts	
Rullo, Fiore R.	Boston

Michigan	
Park, Charles W.	Detroit
New Jersey	
Becker, Marvin C.	Newark
New York	
Goodman, Albert L.	East Rockaway
Murphy, John R.	New York
Schumacher, L. Richard	St. Albans
Wertheim, Arthur R.	Welfare Island
North Dakota	
McArdle, John S.	Minot
Ohio	
Kessler, Margaret F.	Cincinnati
Koenig, Robert P.	Cincinnati
Richardson, Lucille	Toledo
Pennsylvania	
Gill, Robert J.	Philadelphia
Hall, Edgar M., Jr.	Philadelphia
Kelton, Franklin C.	Ambler
Weinhouse, Sidney	Philadelphia
South Carolina	
Boyle, Edwin, Jr.	Charleston
Meakin, Arthur C.	Greenville
Tennessee	
Estes, Paul C.	Murfreesboro
Wofford, Charles P.	Johnson City
Texas	
Madison, Leonard L.	Dallas
Thompson, John Q.	Temple
Virginia	
Robertson, Elmer S.	Richmond
West Virginia	
Patterson, James L.	Logan
Other Countries	
Canada	
Sirek, Otakar V.	Toronto
Zacks, Louis	Peterborough

NEWS OF AFFILIATE ASSOCIATIONS

The NEW JERSEY DIABETES ASSOCIATION (Clinical Society) held a meeting Jan. 30, 1958, in East Orange, New Jersey. Subject of the program was "Clinical Aspects of Insulin Binding Antibodies," by Solomon A. Berson, M.D., Chief of the Radioisotope Service, Veterans Administration Hospital, Bronx, New York.

The Metabolic Section of the Medical Society of New Jersey will hold a meeting in Atlantic City on May 21, 1958, with the following papers and authors scheduled to date: "Treatment with the New Hypoglycemic Agents," by Edward Tolstoi, M.D., New York City; "Some Newer Aspects of the Treatment of Thyroid Disease," by Solomon Silver, M.D., New York City; "Iron Metabolism," by Murray Nusbaum, M.D.; and "Special Aspects of Water Metabolism," by Donald E. Brown, M.D., Hackensack. William Levison, M.D., Newark, is Chairman, and J. John Kristal, M.D., Hackensack, the Secretary of the section for this year.

NEWS NOTES

NATIONAL VITAMIN FOUNDATION APPROPRIATION FOR RESEARCH

The National Vitamin Foundation has announced the appropriation of an additional $61,268 to support basic nutrition studies in the coming year. This brings the total sum appropriated by the Foundation for research to $1,346,316.45, according to Robert S. Goodhart, M.D., Scientific Director. Research projects to be supported in 1958 include probing the link between vitamins and hormones.

MEDICAL EDUCATION WEEK

Medical Education Week will be observed for the third successive year during April 20-26, 1958, it was announced by the American Medical Association. Its objective is to bring to the medical profession and to the public the story of the progress and achievements of the nation's medical schools, and how they plan to meet the challenges of the future.

ADA MEMBERS TO PARTICIPATE IN ACP POSTGRADUATE COURSES

The following members of the American Diabetes Association will take part in postgraduate courses arranged by The American College of Physicians during the spring:

Hyman J. Zimmerman, M.D., Chicago, will be an Officer of Instruction for Course No. 4 entitled "Current Views in the Diagnosis and Treatment of Cardiovascular Diseases in the Child and the Adult," to be held May 12-16 at the University of Illinois College of Medicine in Chicago.

Robert C. Hardin, M.D., Iowa City, Rachmiel Levine, M.D., Chicago, and Charles H. Read, Jr., M.D., Iowa City, will be Officers of Instruction for Course No. 5 entitled "Principles and Practice of Internal Medicine," to be held June 2-6 at the State University of Iowa College of Medicine in Iowa City.

John M. Elliott, M.D., San Francisco, Peter H. Forsham, M.D., San Francisco, Felix O. Kolb, M.D., San Francisco, and George B. Roson, M.D., Palo Alto, will be Officers of Instruction for Course No. 7, entitled "Internal Medicine," which will be given June 16-20 at the University of California School of Medicine in San Francisco.

PERSONALS

ALEXANDER M. BURGESS, M.D., Newport, Rhode Island, LELAND S. MCKITTRICK, M.D., Boston, and ROBERT H. WILLIAMS, M.D., Seattle, participated in the 54th Annual Congress on Medical Education and Licensure held in Chicago, Feb. 8-11, 1958. Sponsors of the Congress were: Council on Medical Education and Hospitals of the American Medical Association, the Advisory Board for Medical Specialties and the Federation of State Medical Boards of the United States. Dr. Burgess spoke on "The Community Hospital in Graduate Medical Education"; Dr. McKittrick on the "Purpose of This Conference"; and Dr. Williams on "Problems in Specialty Training in Medicine and Medical Specialties."

GRACE A. GOLDSMITH, M.D., Tulane University, New Orleans, spoke on "Niacin-Tryptophan Relationships in Man and

Niacin Requirement," at the Symposium on Problems of Human Nutrition, held March 4, 1958, in New York City. The Symposium was sponsored by the Medical College of Georgia and the National Vitamin Foundation in honor of V. P. Sydenstricker, M.D., of the Medical College of Georgia.

FRANKLIN B. PECK, SR., M.D., Indianapolis, was recently granted the title of "Academico de Honor" by the Academy of Medicine and Surgery at the University of Panama. The title previously had been given to only two other medical-research scientists. The honor came to Dr. Peck in conjunction with a lecture before the ceremony and with a clinic he held at Gorgas Hospital, Panama. Dr. Peck recently returned from an extensive tour of Latin American countries where he gave more than thirty lectures, conducted clinics, and visited leading medical scientists and institutions.

Dr. Peck was awarded honorary memberships in the Argentine Medical Association and the Medical Society of Santiago, Chile, and received a citation of honor by the Diabetic Association of Peru. While in Buenos Aires, he attended the fourth Pan-American Congress on Endocrinology and delivered two lectures during this meeting.

OBITUARIES

MAURICE BRUGER, M.D., New York City, was born May 18, 1904, in Montreal, Canada. A medical educator and specialist in the field of metabolism, Dr. Bruger was Director of the Department of Clinical Pathology and Chief of the Thyroid Clinic at University Hospital. He came to New York from McGill University in 1930 as the Oliver Rea Fellow in Medicine at the New York Post-Graduate Medical School and Hospital. He became Associate Professor of Medicine in the post-graduate division of the New York University-Bellevue Medical Center, and was Attending Physician at University Hospital, and a Visiting Physician at Bellevue. Dr. Bruger was co-author of *The Prevention of Disease in Everyday Practice* (1955) and was the author of many scientific papers in the fields of cholesterol and iodine metabolism, hypertension, diabetes, and renal and liver diseases. A member of the American Diabetes Association since 1941, Dr. Bruger was also a member of the American Society of Biological Chemists, Society for Experimental Biology and Medicine, American Institute of Nutrition, American Academy for the Advancement of Science, American Federation for Clinical Research, American College of Physicians (Fellow), Harvey Society, American Society for the Study of Arteriosclerosis, Gerontological Society and New York Academy of Sciences.

DANIEL P. FOSTER, M.D., Detroit, was born Feb. 26, 1892, in Portland, Oregon, and died at the age of sixty-three. Dr. Foster received his B.A. and M.A. degrees from the University of California (1913-18), and his M.D. from Harvard University Medical School in 1922. A member of the American Diabetes Association since 1941, he was Chief of the Department of Metabolism at Henry Ford Hospital, Detroit, from 1924 until 1945. Dr. Foster was a Fellow of the American College of Physicians, a member of The Endocrine Society and of the Society for the Study of Internal Secretions.

JACOB KRIEGER, M.D., Brooklyn, New York, was born Sept. 20, 1891, and died at the age of sixty-four. He received his M.D. in 1913 from Long Island Medical College, and had been a member of the American Diabetes Association since 1953.

BERNARD GILL MCLAUGHLIN, M.D., Washington, D.C., was born July 17, 1926, in Manchester, New Hampshire. Dr. McLaughlin received his M.D. from Georgetown Universtiy in 1951 and served his internship and residency at Georgetown University Hospital. He had been a member of the American Diabetes Association since 1952.

HAROLD ROOSTH, M.D., Tyler, Texas, died Feb. 7, 1957, of a cerebral hemorrhage. He was born Sept. 22, 1915, in the same city, received his B.A. degree from the University of Texas in 1936, and his M.D. degree from the University of Texas in Galveston in 1940. Dr. Roosth interned at St. Vincent's Hospital in Erie, Pennsylvania, and took his residency at John Sealy Hospital in Galveston, 1946-48. He was a member of the Medical Corps during World War II, starting as a First Lieutenant in August 1941, and being discharged in 1946 as a Lieutenant Colonel; he participated in four European Theater campaigns. Dr. Roosth had been an active member of the American Diabetes Association since 1956.

FELIX L. VERDESCHI, M.D., Ozone Park, New York, died at the age of fifty-four. Born in New York City, he received his premedical education at Alfred University, New York, and was awarded his medical degree at the New York Medical College in 1928. Dr. Verdeschi had been a member of the American Diabetes Association since 1954.

CHARLES WILLIAM WARREN, M.D., Rochester, New York, died at the age of fifty-six. A member of the Medical Staff at Rochester General Hospital he was also Assistant Physician, Strong Memorial Hospital, and Assistant Attending Physician, Genesee Hospital. At the University of Rochester School of Medicine, he was Instructor in Medicine. A member of the American Diabetes Association since 1941, he was a Fellow of the American College of Physicians and the American Academy of Allergy. Dr. Warren was Chairman of the Committee on Diabetes of the Monroe County Medical Society, and organized the Diabetes Fair in Rochester in 1953.

GEORGE A. WESTFALL, SR., M.D., Halstead, Kansas, died Sept. 18, 1957. He was born in Harper, Kansas, Sept. 26, 1890. After receiving his M.D. degree from Tulane University in 1913, he became Assistant Superintendent of the Western State Mental Hospital at Supply, Oklahoma. After serving in the U.S. Army during World War I he returned to Harper, Kansas, where he practiced from 1919 to 1929. In 1930 he joined the medical staff of The Hertzler Clinic, where he was Treasurer from 1946 to 1954. He was Chief of Staff of the Halstead Hospital and President of The Hertzler Clinic in 1954 and 1955. Dr. Westfall was a member of The American College of Physicians, and had been a member of the American Diabetes Association since 1941.